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DISCOVERY

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50 YEARS

In 1974, Patrick and Margaret Walsh Came to the Brady and Transformed It

INSIDE THIS ISSUE

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DISCOVERY AND INNOVATION

Pat and Margaret Walsh came to the Brady 50 years ago and transformed it. Patients came to Hopkins from all over the world for the landmark nerve-sparing radical prostatectomy that Pat developed, and surgeons came to Hopkins to learn his innovative techniques for preserving potency and urinary continence. But Pat didn't just focus on surgery; with Don Coffey as the Director of Research, he developed a world-class research program, and the Brady became a powerhouse in the treatment of diseases of the kidney, bladder, and prostate.

Many Walsh-trained urologists went on to careers in academic medicine, and 23 became chairs of urology departments. I am one of them: I was born in 1974, the year the Walshes came to Hopkins. When I came to the Brady as a resident, Pat Walsh was my mentor in meticulous surgical technique, and his successor, the late Alan Partin (page 18), was my mentor in leadership.

The Brady continues to transform the field of urology, as you will see in this issue of *Discovery*. Among many exciting things to tell you about, we welcome Drs. Arvin George as our new Director of Prostate Cancer Programs (page 10) and Ahmed Ghazi as our new Director of Minimally Invasive and Robotic Surgery (page 13). Ahmed's work is revolutionizing how residents and fellows are trained, and even how experienced surgeons can practice in simulated surgery before difficult procedures.

Building on Dr. Walsh's vision, the Brady looks ahead to the next 50 years with great excitement and hope. As always, the Brady's patients and friends are our partners in discovery and innovation. Your support has made many of our efforts possible, and we appreciate you.

Mohamad E. Allaf, M.D.
Jakurski Family Director
The James Buchanan Brady Urological Institute
Johns Hopkins Medicine

COVER STORY

50 YEARS

In 1974, Patrick and Margaret Walsh Came to the Brady and Transformed It.

Fifty years ago, Johns Hopkins Medicine made one of its smartest moves ever. When it came time to find a successor for the Director of Urology, venerable William Wallace Scott, M.D., Ph.D., Hopkins had the foresight to hire a young guy, a brilliant surgeon-scientist, fresh out of his 10-year training journey – a rising star who had also been tapped to be the next Chief of Urology at Harvard.*

As the search committee wrote to the School of Medicine's Advisory Board, Patrick Craig Walsh, M.D., represented "a unique opportunity for bringing into the Johns Hopkins Hospital a young, excellently trained clinician investigator who will be a great stimulus to the future development of the currently outstanding urology program."

And there was a huge bonus: Pat's wife, Margaret ("Peg"), a gifted interior designer, had wowed the search committee, too. At their recruitment dinner, Dean Russell Morgan said, "I don't care if Pat accepts the offer, but Peg has to come." She did, along with Pat and their three young sons.

On July 1, 1974, Walsh, age 36, started work as the third Professor and Director of the James Buchanan Brady Urological Institute, a position he held for thirty years. During his tenure, the Brady became a world-class center for urological patient care, research, and training. At first, though, Pat and Peg had their work cut out for them.

Founded in 1915 by the father of modern urology, Hugh Hampton Young, the Brady had seen better days. The Brady Building itself, along with most of the hospital, had aged without renovation for decades. The full-time faculty in Urology was tiny – just Walsh, Scott, and two junior professors. Within their first ten years, Pat and Peg recruited outstanding faculty and relocated the Brady to the Marburg Building. During this time, Walsh also honed his craft, developing innovative surgical procedures that would transform the field of prostate cancer.

RECRUITING GREAT FACULTY

Walsh's faculty recruits now read like a "Who's Who" of Urology. He appointed Donald S. Coffey, a first-class scientist and legendary teacher and mentor, as the Director of Research. He also recruited Robert Jeffs from Toronto's Hospital for Sick Children to head the new Division of Pediatric Urology; and Ray Stutzman, Chief of Surgery at Walter Reed Army Hospital, to become the Director of Urology at Johns Hopkins Bayview Medical Center. He brought in Fray Marshall from Harvard, Michael Droller from Stanford, and Charles Brendler from Duke as specialists in cancers of the kidney, bladder, and prostate, respectively. Also from Harvard, Lou Kavoussi came to develop the new Division of Minimally Invasive Surgery. (You can read more about the many truly outstanding faculty members in *The Brady: 100 Years*; see link on page 4.)

REVOLUTIONIZING SURGERY

The first radical prostatectomy was performed at Hopkins in 1904 by Hugh Hampton Young. But by Walsh's time, it was rarely performed because of its terrible side effects: impotence, incontinence, and excessive bleeding. Based on anatomical studies, Walsh developed a procedure that created a "bloodless field" – allowing surgeons to see what they were doing! Then, with Dutch urologist Pieter Donker, he discovered the location of the microscopic nerves that controlled erection.

On April 26, 1982, Walsh performed the world's first purposeful nerve-sparing radical prostatectomy and revolutionized the treatment of prostate cancer.

Within a decade, the statistics changed dramatically: in 1982, only 7 percent of men with prostate cancer underwent surgery, but by 1992, with the development of PSA screening to identify more men with curable disease, this safe procedure had become the most common treatment for prostate cancer in the U.S. for men ages 50–70. By 2002, deaths from prostate cancer had declined by 33 percent – greater than seen in any other cancer over the same time period.

This operation also transformed the Brady and Johns Hopkins. Before 1982, fewer than a dozen radical prostatectomies were performed each year. But by 1997, Walsh's procedure was the most common inpatient operation at the Johns Hopkins Hospital, with over 1,000 cases performed each year. Interest in the procedure grew as urologists from around the world came to watch Walsh and learn his techniques. For years, Walsh worked to make the operation even better, perfecting his surgical technique through meticulous follow-up and analysis of his patients' outcomes.

Walsh cared deeply for his patients and still does today. He has given every patient his home telephone number. He spoke to all patients he operated on (4,569 men) every three months for the first year following their surgery, and longer as needed. He coached them to recovery, and every year sent them a letter inquiring about their status. He also felt he had a major responsibility to teach urologists how to do this operation well.

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ON THE COVER

Dr. Patrick Craig Walsh by Peter Egeli, 1998. Image Courtesy of the Alan Mason Chesney Medical Archives.

*Yes, Pat Walsh was supposed to go to Harvard. At age 27, fresh out of his internship at Harvard, he had been told by his mentor, Francis Moore, M.D., the legendary Surgeon-in-Chief at the Peter Bent Brigham Hospital and the Mosley Professor of Surgery at Harvard Medical School, that he wanted Walsh to be the next Elliot Carr Cutler Professor of Surgery at Harvard and Chief of Urology at the Brigham. Moore then sent Walsh on a nine-year transcontinental training journey that would hone his already impressive surgical skills and provide the opportunity for pioneering molecular endocrinology research. Among other scientific achievements, Walsh was the first to show that cyproterone acetate blocked the stimulatory effect of adrenal androgens on prostate growth. A decade later, this finding was used on a widespread scale in complete androgen blockade of the prostate, and today, powerful antiandrogens have been shown to prolong life in men with advanced prostate cancer.

Pat and Peg Walsh: *Dr. Walsh is looking sharp in the Brady tie — which Peg designed! She based the logo on the Marburg building's cupola, with its double-hung windows that spell "BRADY." The Brady's colors, chosen by Peg from the historic building's red brick and grey grouting, were also used as accent colors throughout the Marburg's interior.*

He installed excellent video equipment in the operating room so the many visitors who came to watch him operate could see deep into the pelvis.

This turned out to be useful in other ways. Recognizing that small differences in surgical technique could have a major impact on outcomes, Walsh began videotaping his cases, and even spent one summer vacation examining them, stopping the video frame by frame. This enabled him to identify slight variations in technique that significantly enhanced recovery. In 2004, he produced a detailed DVD of the operation, and with generous support from the Mr. and Mrs. Robert C. Baker Family Foundation, he distributed 50,000 copies worldwide free of charge to all urologists who sought one. Today, this video remains a valuable resource for urologists without access to a surgical robot.

MOVING THE BRADY

When Walsh arrived in 1974, the Brady Building had just 13 private beds for patients, and even the single rooms shared a bathroom. Two architectural reviews determined that it would be impossible to renovate the facility for modern inpatient care. The Brady had to be relocated.

Around this time, the Marburg Building – built in 1889– was vacated. With the assistance of William Scott, who raised $2 million dollars, and with Peg overseeing the renovation, this became the Brady's new home. With more inpatient beds, modern laboratories, a dedicated conference room and library, the space was updated beautifully and thoughtfully. Peg's elegant design captured the spirit of the historic architecture. The building opened in September 1982, five months after the first nerve-sparing procedure – perfect timing, as patients had started coming to Hopkins from all over the world for radical prostatectomy.

With an abundance of patients, outstanding faculty, and excellent facilities, discovery flourished both in the clinic and in the laboratory. Soon, the Brady was ranked number one by *U.S. News & World Report*. This also attracted outstanding candidates to the residency program.

HELPING DOCTORS AND PATIENTS WORLDWIDE

During Walsh's 30 years as Director, 62 Urology residents were trained: 87 percent established careers in academic medicine, and 23 became directors of esteemed Urology departments at academic hospitals around the country. But his impact in teaching has grown far beyond the Brady. For 25 years, Walsh was editor-in-chief of the major four-volume, 4,000-page textbook of urology, *Campbell's Urology*, nicknamed "the bible of urology," which was renamed *Campbell/Walsh* in his honor. For 15 years he served on the editorial board of the *New England Journal of Medicine*. Together with Janet Worthington, Walsh authored two bestselling books on the prostate and prostate cancer for laypeople. He has authored/coauthored 885 scientific publications. In 2023, Walsh was identified as the most cited urologist in the world, based on the number of influential publications he has authored.

In recent years, Walsh has been invited to give many talks to young physicians about how to make discoveries. He tells them to listen to their patients. If they are asked a difficult question or faced with a challenging fact (like the first patient who told Walsh that he was potent after his radical prostatectomy at a time when this seemed impossible), this is their opportunity for discovery! Also, he advises, learn from Albert Einstein, who said: "The person who follows the crowd will usually go no further than the crowd, but the person who walks alone is likely to find himself in places no one has ever seen before."

And finally: "Even if they follow all that advice, they will not be successful without the most important ingredient: a partner in life who inspires and embraces their dreams and is willing to accept the sacrifices that will be necessary." Pat has that partner, and the Brady would not be the same today, had it not been for Peg.

A fund has been established in celebration of Dr. Walsh's 50 years at the Brady, to honor his lifetime dedication to surgical advances, education and training, and to support the future of innovation in urologic surgery. For more information, please call 410-955-8434, or contact bradydevelopment@jhmi.edu. ■

TO LEARN MORE:

Celebration of Patrick and Margaret Walsh's 30 years of contributions to the Brady as of October 30, 2004
www.youtube.com/watch?v=fqWf5h7GoS4

The Brady: 100 years: A History of the James Buchanan Brady Urological Institute at Johns Hopkins
https://jscholarship.library.jhu.edu/items/eedd260b-916b-48cf-9241-73f68dc7505f

Alpha Omega Alpha Leaders in American Medicine: Patrick C. Walsh Interview (1999)
www.hopkinsmedicine.org/brady-urology-institute/about_us/history/index.html#videos

A Fortunate Misdiagnosis

More than 60 years ago, a beautiful friendship began with a life-changing second opinion.

Dr. Ralph "Tip" Warburton, an internist from Ohio, was told by a local doctor that he had prostate cancer. In the late 1950s, this was devastating news. Prostate cancer was commonly detected at a later stage than it is today, and treatment was not great. Radiation was not yet powerful enough to cure the disease, and surgery – before Patrick Walsh, M.D., developed the anatomical "nerve-sparing" radical prostatectomy – was brutal, leaving every man impotent and incontinent. Not a diagnosis any man wanted to receive.

Warburton and his wife, Esther, came to the Brady for a second opinion, and what a good thing they did! Distinguished urologist, Hugh Judge Jewett, M.D., one of the pioneers of urologic oncology, determined that Dr. Warburton did not have prostate cancer at all; instead, he had an infection. "My father and mother were there for about a week," says Phil Warburton, Ralph and Esther's son. "That's how it all started."

The two doctors and Esther, who had been Ralph's first nurse, "soon found that they shared a passion for excellence in medicine," says Walsh, "and this formed the foundation of their deep and lasting friendship." Walsh, who was then the new Brady Director, met the Warburtons in 1975; when Jewett retired, Walsh became Ralph's urologist. They became great friends, as well," says Phil. "My father sent patients to Dr. Walsh because he respected him so much."

"If we were all that way, the world would be a better place."

In his own practice in North Canton, Ohio, Ralph Warburton was beloved. Five thousand people came to the reception when he retired, says Phil. At one point during the event, Ralph was sitting down and one of his patients came to talk to him. "She was kneeling in front of him, her hands in his, tears coming down her cheeks because she wouldn't have him to talk to anymore." That was the relationship he had with his patients: they loved him, and he loved the patients. He would call them on Sunday afternoons and visit them in hospitals and nursing homes, even when he was retired. "He was dedicated to the practice of medicine. Love was a big part of his life – love for people. If we were all that way, the world would be a better place."

The Warburton family has a long history of giving back, particularly to initiatives that inspire and nurture compassionate medical care. In the 1970s, Ralph founded the nonprofit North Canton Medical Foundation to provide high-quality, accessible care. In 1999, Ralph and Phil formed The Esther Lewis Warburton Patient Education Initiative to help patients become advocates for themselves and their families. When Ralph died in 2010, the Warburton Family Foundation, led by Phil, his wife, Sally, and their two daughters, Carrie Warburton Montalto and Betsy Warburton Downs, honored his legacy at Johns Hopkins, Case Western Reserve University School of Medicine, and the Mayo Clinic. In addition, with Victor Montori, M.D., Phil founded The Patient Revolution, a global organization to foster careful and kind care.

In 2011, a major gift from the Jewett estate and Warburton Family Foundation established the Warburton-Jewett Fellowship in Urologic Oncology at the Brady. The two-year fellowship program includes a year of extensive academic research, specializing in urologic oncology, and a year of clinical learning, including surgical practice. The Fellowship's mission is to inspire young doctors to practice exceptional, compassionate care after the examples set by Drs. Warburton, Jewett and Walsh. In 2023, the Warburton family added to this gift.

"Quite a Life"

Ralph Warburton "had quite a life," says Phil. His beginnings were humble, says Betsy Warburton Downs. "One Christmas, his best gift was an orange. They didn't have much." But the family said that Ralph had a rabbit's foot – "he always had luck and hard work on his side," and he built a successful practice. "That's part of why we reached out to Johns Hopkins. He wanted to give back from what he had achieved, to support the things that meant something to him. He came from nothing, and never forgot it. He loved giving back and giving to others and being able to share in his success."

Downs remembers that her grandfather always wore a suit, was cheerful, and "whistled everywhere he went." Carrie Warburton Montalto notes that when Ralph Warburton walked around town, he always stopped to talk to people. "Everyone knew him. Connecting with people, caring for one another, and loving your neighbor. That's how he lived his life and how he built his career."

Montalto continues: "My grandfather's relationship with Dr. Walsh was really important." Both were from nearby towns in Ohio: Canton and Akron. Both were paperboys, and both were graduates of the same medical school – Case Western Reserve University in Cleveland. In addition, "my grandfather really valued the excellence that Dr. Walsh brought to his practice, and he wanted specifically to give to Johns Hopkins because of that friendship."

Often, adds Montalto, people give "not so much because of the institution, but because of the *people* in the institution who create the relationship. We're doing this because of Dr. Walsh and the esteem my grandfather had for him, both as a doctor and as a friend." ■

Narrowing the Racial Gap in Prostate Cancer

The likelihood of this disease occurring is 70- to 80-percent greater in Black men, and Black men are more than twice as likely to die from prostate cancer than White men."

"Despite advances in early detection, prevention, and treatment, Black men in the U.S. remain disproportionately affected by prostate cancer," says urologist Arthur Burnett, M.D., the *Patrick C. Walsh Professor of Urology*. "The likelihood of this disease occurring is 70- to 80-percent greater in Black men, and Black men are more than twice as likely to die from prostate cancer than White men."

Hoping to address this disparity, Burnett and a group of Black urologists and business and academic colleagues

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established the Consortium on Disparities of Urologic Conditions (ConDUC), a non-profit organization, in 2017. "To narrow this racial gap," Burnett says, "a longitudinal database comprising predominantly Black men with all stages of prostate cancer nationwide is now in the works."

An executive board member of ConDUC, Burnett is spearheading the participation of Johns Hopkins as a clinical site involved in this registry, called SCOPE (Scientific Consortium on Prostate Cancer Education). "We anticipate that SCOPE will play an important role in enrolling more Black men in clinical research studies, and heightening the diagnosis, evaluation, and treatment of prostate cancer in this population, ultimately improving their prostate cancer outcomes." ■

Lowering the Risk of Recurrent Prostate Cancer

Exciting results from a Hopkins-led study have catapulted a lowly immune system protein into the spotlight as a promising new target for prostate cancer immunotherapy.

B7-H3 is an immune "checkpoint," a tiny padlock that restrains the body's powerful immune cells and prevents them from fighting cancer. "B7-H3 is expressed on the majority of prostate cancer cells," says Eugene Shenderov, M.D., Ph.D., Co-Director of the Johns Hopkins Prostate Cancer Multidisciplinary Clinic.

Could blocking this protein with a checkpoint-inhibiting agent be a game-changer for some men with high-risk prostate cancer? This was the focus of a recent Phase II clinical trial led by Shenderov, urologist Mohamad Allaf, M.D., and medical oncologist Emmanuel Antonarakis, M.D. (formerly at Hopkins, now at the University of Minnesota).

In the trial, 32 men with high- or very high-risk prostate cancer who were scheduled for radical prostatectomy at the Brady received neoadjuvant therapy: six weekly infusions of a B7-H3-targeted antibody called enoblituzumab. They had surgery two weeks after the last dose, and their prostate tissue was examined.

Did enoblituzumab have an effect? It sure did: a year after surgery, 66 percent of high-risk or very high-risk patients had an undetectable PSA.

Did enoblituzumab have an effect? It sure did: "21 patients (66 percent) had an undetectable PSA 12 months after surgery," says Shenderov. Moreover, "in some men, enoblituzumab therapy appeared to lower the Gleason grade group between biopsy and prostatectomy." This finding is preliminary, he adds, and needs to be proven in larger trials. But what is clear is that the tumor microenvironment showed significant changes in activity, particularly in the presence of cancer-fighting T-cells and other robust immune cells. This work was published in *Nature Medicine*.

"Enoblituzumab therapy offers a promising new route for potentially minimizing recurrent disease after prostate cancer surgery for men with high or very high-risk disease," says Shenderov. Based on these results, Shenderov and colleagues at Harvard, Northwestern, Minnesota, and Mayo Clinic have designed a larger randomized trial for men with high-risk localized prostate cancer: The Help Elucidate & Attack Longitudinally (HEAT) Prostate Cancer Trial (NCT06014255). Enrollment will begin in February 2024. ■

Looking for Bad Genes

Scrutinizing 25,000 genes in 8,000 men with prostate cancer.

Remember the childhood game of Telephone? A sentence such as "The sheep-dog herded cattle into the barn" whispered from person to person somehow gets misinterpreted again and again, resulting in something like: "The sheep had kettle corn!"

The same thing could easily happen with our DNA as it makes copies of itself. But it usually doesn't, because of our very own safeguards: *DNA damage repair (DDR) genes*. They are the quality-control supervisors, the tiny inspectors that help keep genetic mistakes from repeating themselves. "The cell's ability to execute high-fidelity repair of DNA damage is particularly important in preventing cancer," says molecular geneticist William Isaacs, Ph.D., the *William Thomas Gerrard, Mario Anthony Duhon, and Jennifer and John Chalsty Professor of Urology*.

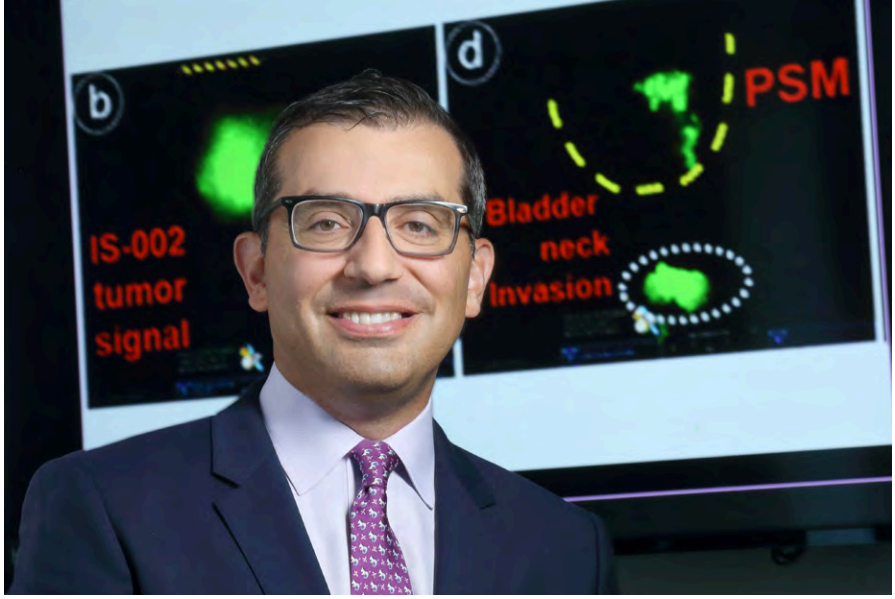
Unfortunately, these genes are not foolproof, and when DNA damage repair genes don't do their jobs, cancer may develop. Of all the genes known to confer a strong inherited risk of prostate cancer, only one – *HOXB13*, discovered by Isaacs and colleagues – is *not* a DDR gene!

The handful of mutated genes most strongly linked to prostate cancer can be inherited from either the mother or father, and are also linked to breast, ovarian, colon, and other cancers. These include *BRCA2, ATM, CHEK2, PALB2,* and *MSH2*.

But there are almost certainly other mutated DDR genes tied to prostate cancer risk, and Isaacs is looking for them, along with Brady scientists Jun Luo, Ph.D., and Shawn Lupold, Ph.D. "We are interested in relatively novel DDR genes that have not previously been linked to increased risk for prostate cancer – or any other cancers," says Isaacs.

How does one look for a gene? With a lot of hard work! "We use next-generation DNA sequencing to examine the protein-coding sequences of each of the cell's 25,000 or so genes, including all DDR genes, to detect mutations of interest," says Isaacs. The team is doing this in an analysis of sequence data from more than 8,000 men with prostate cancer. They have found some promising candidates for further study: "A series of DDR genes, including *SPIDR, SWS1, SWSAP1, MMS22L, c17orf53*, and *TONSL*, are of particular interest. They all harbor rare, inherited loss-of-function mutations that cause significant problems in the cell's ability to repair its DNA, which can ultimately result in the cell's transformation from normal to cancerous." The investigators anticipate that some of these genes will be added to genetic tests, "with the beneficial result that more men at high risk for prostate cancer, particularly more aggressive disease, can be identified and followed closely."

This work is supported by the Patrick C. Walsh Hereditary Prostate Cancer Program and its generous contributors. ■



***Allaf**: If the trial proves successful, "this potentially ushers in a new era of surgery that's molecularly based."*

Innovations in Prostate Biopsy and Surgery

Molecular-directed prostatectomy, refinements in control of urinary continence, and a comparison of prostate biopsy approaches: clinical trials that will shape prostate cancer diagnosis and treatment.

Important clinical trials related to prostate cancer are under way at the Brady, and urologist Mohamad Allaf, M.D., the *Jakurski Family Director* and *Urologist-in-Chief*, is helping lead them.

"Trials are really what inform clinical care," says Allaf, "but surgeons don't perform a lot of clinical trials. In fact, clinical trials in urology are rare – and these are all potentially practice-changing." Two of the trials are related to the nerve-sparing radical prostatectomy procedure, developed at the Brady by Patrick Walsh, M.D., and a third is a comparison of two forms of prostate biopsy.

Looking for stray cancer cells with a PSMA tracer: PSMA tracing is, on a molecular level, basically like using a black light to make colors glow – and what lights up is prostate cancer. PSMA (prostate-specific membrane antigen) is a protein that sits on the surface of prostate cancer cells. Hopkins physician-scientist Martin Pomper, M.D., Ph.D., and colleagues figured out how to target it using a small molecule attached to a radioactive tracer, and this molecule was FDA-approved for PSMA-PET imaging.

Now, building on this technology, Intuitive Surgical (the company that makes the DaVinci device used in robotic prostatectomy) is sponsoring a Phase II clinical trial to see whether a PSMA-targeting agent can make a difference in prostatectomy. Hopkins is one of four centers participating in the trial, along with UCSF, Memorial Sloan-Kettering, and the Mayo Clinic.

"The agent is injected the day before surgery," says Allaf, "and then we can turn on an infrared camera during surgery, and we're able to see the fluorescence. The cancer appears green on the screen." If the trial proves successful, "this potentially ushers in a new era of surgery that's *molecularly based*. We're able to see the tissue as we normally do during surgery, and also to discern something about it molecularly."

At each step in surgery, "we turn on the infrared camera, and if we see the green, not only can we react to it and cut wider, but we mark the tissue with ink," so pathologists can double-check the results of the tracer.

Allaf has side-by-side pictures of the same prostate taken during surgery. There is a tiny dot of green. "It's just a little thing, but that's how a recurrence starts." In this case, the green was in tissue that was already earmarked for removal. "But if it had not been, we would have taken it out."

Optimizing the recovery of urinary continence: One of the most significant consequences of radical prostatectomy is the temporary loss of urinary control. This happens because the urethra, the tube that carries urine from the bladder out of the penis, runs through the prostate, and must be cut and then reattached after the prostate is removed. In an NIH-funded, multicenter clinical trial just getting started, prostatectomy patients will be randomly assigned to one of two slightly different surgical approaches to preserving urinary continence during robotic prostatectomy, and then followed for a year.

Which biopsy is better? In another NIH-funded clinical trial, which has just ended, "biopsy-naïve" men (who have never had a prostate biopsy) were randomly assigned either to undergo the traditional *transrectal* biopsy, which reaches the prostate through the rectum, or the *transperineal* biopsy, which goes through the perineum (the area of skin between the scrotum and rectum). Allaf is one of the Principal Investigators, along with Brady alumni Edward "Ted" Schaeffer, M.D., Ph.D., now at Northwestern, and Jim Hu, M.D., M.P.H., now at Cornell.

"Which form of biopsy is better? That's a big question today, given that over one million prostate biopsies are performed a year in the U.S.," says Allaf. The investigators found that the rate of cancer detection between the two approaches was the same. However, the risk of infection was not: close to 2 percent in the transrectal biopsy group "despite antibiotics and a rectal swab," versus 0 percent in the transperineal group. The study's results are being submitted for publication.

To find out more about clinical trials at the Brady, please go to clinicaltrials.gov. *Note: Look for trials of "prostatic neoplasms."* ■

Galansky: *"All physicians have the power to be advocates." She is the Brady's third H. Logan Holtgrewe Legislative Fellow.*

A Passion for Advocacy

The AUA's selection committee was impressed with Galansky's "unmatched understanding of public policy."

"All physicians have the power to be advocates," says Brady resident Logan Galansky, M.D., "for their patients and practices, for the future of the specialty, and for research and innovation." And yet, "for too long, doctors have taken a back seat to that. We do our training for years to help cure or mitigate a whole range of medical maladies, but there are economic, social, and political factors that affect patient care, too."

Galansky has been named the American Urological Association (AUA)'s 2023-2024 H. Logan Holtgrewe Legislative Fellow. This means, in addition to seeing and treating patients, she participates in meetings of the AUA's Public Policy Council and Legislative Affairs Committee, its annual Urology Advocacy Summit, and the Brandeis University Executive Leadership Program in Health Policy & Management. She will also work for a month in a legislator's office in Washington, D.C.

The AUA's selection committee was impressed with Galansky's "unmatched understanding of public policy." How did she develop this? "I took a nontraditional, circuitous route to medicine," she says. After graduating from Pomona College in California, Galansky worked as a senior research analyst for a health care consulting firm and on Capitol Hill as a Senate intern. During this time, "I saw a large gap between what policymakers were saying and doing and what was actually feasible and pragmatic for clinical care." She also wanted to help patients one-on-one, so she went to medical school at the University of Chicago Pritzker School of Medicine.

Now she is working to bridge this gap, taking care of patients *and* helping the broader practice of medicine. "The AUA sends a survey to all its members to set a list of priorities for the year," she explains. Based on what practicing urologists see as important issues, the AUA sets national advocacy goals. These include "getting Medicare coverage for PSA screening; more aid for urologic trauma for Veterans; better screening for underrepresented minorities with prostate cancer; more clinical trials relevant to urology; and surgical care of pediatric urology patients with disorders of sexual differentiation." Then there are issues that span all of medicine, including: "some of the regulations that really contribute to limiting patient care and physician burnout; improving prior authorization, Medicare payment structures; drug pricing; step-up therapy; and rural access to care. All of these things affect urology patients just as much as any other."

Galansky is the Brady's third Holtgrewe fellow. She credits the support of her mentors, Mohamad Allaf, M.D., Arthur Burnett, M.D., and John Gearhart, M.D. "I've had a wonderful experience at the Brady. I'm incredibly thankful that I get to do my training here. My goal is to be a good doctor and a good surgeon, and I'm also passionate about bringing physicians' voices to the table." In urology, "we have seen tremendous advances in treatment, thanks to Dr. Walsh and others at the Brady. We should have that same intensity and vigor in how we advocate for them in a legislative sense." ■

WHO WAS LOGAN HOLTGREWE?

Urologist H. Logan Holtgrewe, M.D., joined the Brady faculty in 1988. Before this, he was in private practice in Annapolis, MD, where he became well-known as an outstanding urologist and scholar. A member of the AUA's executive committee, he became the AUA's spokesman in the area of urologic health policy and socioeconomics. Patrick Walsh, M.D., remembers Holtgrewe as "one of the most active part-time teachers at the Brady. Ever faithful, you could count on him attending Grand Rounds every week, always sitting in the same seat – second row on the right next to the wall. He rarely spoke without being asked a question, but his answers were golden, well thought-out and based on years of experience and education." Holtgrewe was elected President of the AUA in 1992, and in 2001, he received the AUA's highest honor, the Ramon Guiteras Award, for his outstanding contribution to the art and science of urology. That year, he was also made a full Professor of Urology at the Brady. Prior Holtgrewe Fellows from the Brady are Kevin Koo, M.D., M.P.H., M.Phil., in 2018, and Cary "CJ" Stimson, Jr. M.D., J.D., in 2015.

Salvage Radiation after Prostatectomy: Watch the PSA!

To minimize risk of metastases, treat with salvage radiation while PSA is below 0.5.

If PSA becomes detectable and starts to rise after prostatectomy, salvage radiation can still cure the cancer. But exactly when should a man get it? This has been the subject of debate, says radiation oncologist Daniel Song, M.D., Co-Director of the Brady's Prostate Cancer Multidisciplinary Clinic. "Should patients receive radiation while their PSA is very low but detectable, or is a wait-and-see approach better?"

In a recent study, Song and colleagues answered this question – and their findings, published in *Prostate*, could be practice-changing. "We analyzed the data on nearly 400 patients who were treated with salvage radiation at Johns Hopkins," Song says. "Not unexpectedly, patients who had lower Gleason scores and absence of seminal

vesicle invasion did better than those who did not." However, they found the strongest predictor of whether a man's PSA would keep going up after salvage radiation was his PSA level before radiation treatment.

"Men who received treatment before their PSA rose above 0.5 were 60 percent less likely to have long-term PSA failure." And even better: "These men were also about 40 percent less likely to have cancer found in the bone or lymph nodes" (better metastasis-free survival). ■

How PIN Turns to Prostate Cancer

If you've had a prostate biopsy, you may have seen the words "prostatic intraepithelial neoplasia (PIN)" on the pathology report. What is it? Based on years of study, much of it led by Brady scientists, "we recognize PIN as a warning sign of cancer in the making – a precursor lesion," says Vasan Yegnasubramanian, M.D., Ph.D., Professor of Oncology and Co-Associate Director of Precision Oncology at the Kimmel Cancer Center.

What exactly happens to change PIN from a precursor to cancer? To find out, Yegnasubramanian and investigators William Nelson, M.D., Ph.D., and Angelo De Marzo, M.D., Ph.D., looked at molecular alterations to a gene called *GSTP1* (pronounced "GST-pie"). *GSTP1* is a chemical fire extinguisher; it dampens the potential fire of inflammation and keeps it from damaging DNA. But in most men with prostate cancer, *GSTP1* is disabled early on by a series of chemical changes, a process called methylation.

"We dove deep into the DNA," says Yegnasubramanian, "and an intriguing pattern emerged" amid the intermingled cancerous, PIN, and healthy cells. "The amount of DNA methylation in *GSTP1* gradually increased from healthy to cancerous cells," shutting off the fire extinguisher. "This stepwise increase was clearly evident as we moved from normal or inflamed tissue to pre-cancerous PIN tissue, with nearly complete methylation in the full-blown cancerous tissue."

A new biomarker test for prostate cancer may result from this work. "These methylation changes could serve as a telltale sign of the earliest stages of prostate cancer." ■

Who Can Safely Remain on Active Surveillance?

New studies provide guidance.

When is active surveillance (AS) safe, and when is it better to seek curative treatment for prostate cancer instead? Findings from recent Hopkins-led studies provide guidance for men with specific biopsy findings. This work was published in the *Journal of Urology*.

Perineural Invasion (PNI)

"Perineural invasion (PNI) is a term used to describe cancer invading the space surrounding small nerve fibers within the prostate," says urologist Christian Pavlovich, M.D., the *Bernard L. Schwartz Distinguished Professor in Urologic Oncology* and Director of the Prostate Cancer Active Surveillance Program. Most men with favorable-risk prostate cancer – Grade Group 1 (GG1; Gleason pattern 3+3, the lowest grade) – don't have PNI.

Thus, says Pavlovich, "it is a significant finding." In one study, Pavlovich and colleagues found that the presence of PNI on surveillance biopsy was associated with a greater chance of the cancer turning more aggressive during surveillance. "In addition, PNI was associated with prostate cancer actually being found outside the prostate when it came time for radical prostatectomy." However, he notes, the presence of PNI did not impact the long-term prognosis of these patients "because the surgery was thankfully curative."

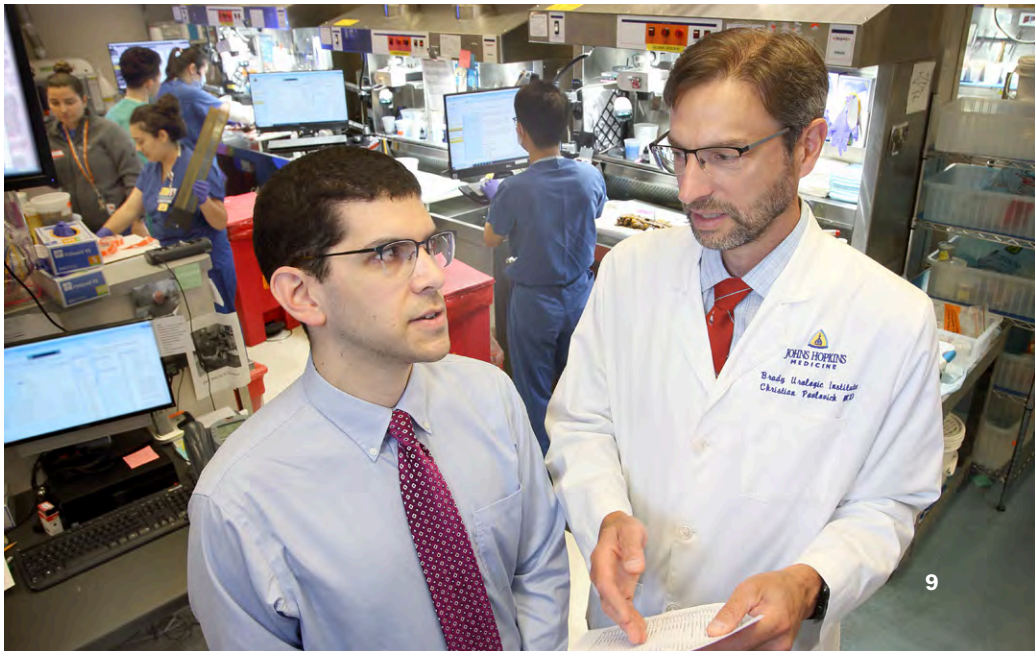
Grade Group 2 Cancer

What happens if you're diagnosed with GG1 cancer, you begin AS, and in a follow-up biopsy, Grade Group 2 (GG2; Gleason pattern 3+4 or 4+3) cancer is found? "When this happens, men often leave AS," says pathologist Ezra Baraban, M.D. But do they have to?

In a second study, Baraban and colleagues sought to identify subgroups of men "who can safely remain on AS," even though they have some GG2 cancer. They studied the prostate tissue of men who started on AS but eventually had prostatectomy. "We found that 57 percent of men who were reclassified to GG2 showed favorable pathologic findings at prostatectomy." In fact, "GG2 patients with low PSA density and without PNI had a lower risk for adverse pathology at prostatectomy than GG1 patients who did have these risk factors. Therefore, reclassification to GG2 alone should not disqualify men from continuing on AS."

Pathological findings that signified higher risk included having a percentage of Gleason pattern 4 approaching 50 percent and large cribriform morphology or intraductal carcinoma. "Conversely, in the absence of other worrisome findings, patients with low PSA density and without PNI are particularly suitable candidates for remaining on active surveillance despite reclassification to GG2." This is reassuring news for men with favorable intermediate-risk cancer on AS. ■

Baraban and Pavlovich: *Even if some Grade Group 2 cancer is found, some men can safely remain on active surveillance.*



Focal Therapy: Killing the Cancer, Not the Prostate

Focal therapy, although not the standard of care, is emerging as a way to treat localized prostate cancer in carefully selected patients. The Brady is proud that one of the leaders in this field, urologist Arvin K. George, M.B.B.Ch., is now our new Director of Prostate Cancer Programs. He joins our faculty from the University of Michigan.

Focal treatment is just one part of George's clinical practice, which spans the diagnosis and management of prostate cancer and other genitourinary cancers; he is an expert surgeon who performs robotic prostatectomy and kidney surgery. His research focuses on the use of imaging and biomarkers in diagnosis, risk stratification, and management of prostate cancer.

Why is focal therapy a tricky subject?
Prostate cancer is a *multifocal disease*: like dandelions in a field, cancer can spring up in several places within the prostate at the same time. That is why the gold standard for localized disease is to treat the entire prostate through surgery or radiation.

Focal therapy – killing, or ablating, only the known spot or spots of clinically significant cancer within the prostate – has been around for decades in various forms; the most common approaches are cryo (freezing) therapy and high-intensity focused ultrasound (HIFU), and other technologies are emerging. But for years, urologists have had questions about the idea of focal therapy itself, including:

- What if you kill cancer in one spot, but miss another tiny site or sites of cancer?
- Urine exits the body through the urethra, which runs right through the prostate, like a road through a tunnel. To protect it during focal therapy, doctors maintain its normal temperature with either a heating or cooling tube. What if there is cancer near the urethra that is also spared?
- What if one spot of cancer is ablated, but a new one starts to grow? Can the prostate tolerate multiple courses of the same type of focal therapy, should a different approach be used, or should the patient shift to surgery or radiation?

Why is Hopkins now investigating and offering focal therapy? What has changed?
First and foremost, says George, the reason is imaging. "The better imaging gets, the better and more precise our treatments become." *Improvements in MRI have been game-changing.* "We can see where a lesion is, how far it extends, and apply a treatment to just that area." There is a potential for PSMA-imaging technology to play a role in the treatment of localized disease (see story on page 8), although to date it has not routinely been used in patients who are considering focal therapy.

"The better imaging gets, the better and more precise our treatments become."

Risk stratification has gotten a lot better, too. PSA density, biomarker tests like the 4K score and Prostate Health Index (PHI,) and molecular pathology findings (from the biopsy tissue) help doctors create a "profile" of the cancer, to evaluate its potential to be aggressive or more slow-growing.

Thus, says Mohamad Allaf, M.D., "as we are understanding the biology of the disease more, and our ability to see the cancer has gotten better – even though MRI and PSMA-PET aren't perfect – there may be a role for focal therapy." This remains to be proven, he adds, and "Arvin is perfectly suited to doing this. Doctors out in the community are already providing focal therapy, and somebody needs to take the lead to study it in a very rigorous way, tracking the cancer control long-term. We see the Brady as a steward of treatment and as a leader in defining the role of focal therapy. The unique thing Arvin brings is the academic rigor to study and implement focal therapy and anything image-guided within prostate cancer, including new MRI fusion transperineal biopsies."

One important priority is improving the public understanding of focal therapy, says George. "We definitely have some bridges to rebuild," because of physicians worldwide over the last 20 years who have not been as responsible or, regrettably, as skillful as they should have been. "We didn't know what we didn't know. There was a learning curve to this new technology: how we apply it, and how we follow

George: *With rigorous follow-up, focal therapy can be a good option for carefully selected men with localized prostate cancer.*

men afterwards. We have some clarity regarding this with updated surveillance protocols, but we still have much to learn!"

That said, he adds: "Some practitioners of focal therapy out there have been frankly sketchy," he says, "providing inadequate coverage of the cancer, exorbitant out-of-pocket costs, no follow-up, learning on patients as the technology developed, causing fistulas and other complications. We are still suffering from that hangover of offshore treatments and cash pay."

But focal therapy is not the same today as it was then. With rigorous follow-up, George says, focal therapy can be a good option for some men with localized cancer. "Tens of thousands of cases of focal ablation have been performed," he says. "While we have less data than that, we do have five- to seven-year median outcomes on more than 1,300 patients that have been published." He believes focal therapy is here to stay. "It's all about choosing the right patient."

Right now, the "sweet spot" for focal therapy is a patient with intermediate risk. "Less aggressive cancer may require no treatment at all, and more aggressive disease requires more aggressive treatment." The ideal patient "has cancer that is visible on imaging but is not near vital structures like the urethra, rectum, or neurovascular bundles, and has no high-risk features such as extracapsular extension or seminal vesicle invasion."

George is the Principal Investigator of two clinical trials of focal therapy. One is the PRESERVE study, involving prostate tissue ablation through irreversible electroporation (IRE). IRE is largely "athermal." It doesn't use either heat or cold; instead, it generates an electrical field across tissues between two electrodes. The electricity creates holes in the cells on a microscopic level, causing them to die. "Because IRE doesn't harm the scaffolding, or connective tissue, theoretically, it can treat closer to the nerves." The other study is the VAPOR 2 trial, using water vapor to destroy tissue.

This work fits right in with the Brady's history of "redefining treatment for prostate cancer across the globe in surgery, in active surveillance, and imaging through PSMA-PET," he continues. "I'm hoping that we can have a similar impact on the field from the perspective of ablation. This is an extremely hopeful time for men with prostate cancer." ■

Inflammation, Club Cells, and Prostate Cancer

What's wrong with inflammation? Sometimes, it is good. For example, when you skin your knee, inflammation protects your body from bacteria and germs. But chronic inflammation can lead to changes in DNA. In fact, adding to discoveries previously made at Hopkins, scientist Karen Sfanos, Ph.D., M.S., and colleagues have found further evidence that chronic inflammation in the prostate may serve as a risk factor for the development of high-grade prostate cancer.

How does inflammation lead to dangerous cancer? This was the focus of a recent study published in the *Journal of Pathology* by Sfanos and her lab. "We found that cells in the vicinity of chronic inflammation in the prostate start to mimic a cell type in the lung, called club cells." Like many good things that are hijacked by cancer, club cells normally are protectors, Sfanos explains. "They help guard the lungs from cellular damage and infectious pathogens." This phenomenon of cells altering their identity and function is termed cellular plasticity, or lineage plasticity. "Importantly, lineage plasticity is linked to high-risk cancer as well as to cancer drug resistance."

Oddly, prostate cells in the vicinity of chronic inflammation start to mimic a cell that's normally found in the lung.

In the study, the investigators found the club cells were present in a lesion called proliferative inflammatory atrophy, or PIA (first described at Hopkins by Angelo De Marzo, M.D., Ph.D. and colleagues). PIA is associated with chronic inflammation in the prostate and is a harbinger of trouble: "Multiple recent studies indicate that the cells in PIA exhibit some properties of cancer cells and are more prone to DNA damage that can initiate a prostate cancer," Sfanos says.

Pathologic studies have found that prostate club cells do not normally exist in the peripheral zone, the region where prostate cancer most often begins. But they were plentiful in tissue samples from men with prostate cancer – particularly in men who had high-grade prostate cancer. "Of keen interest, these cells were also present in the vicinity of PIA lesions that were transitioning to early prostate cancer!"

A hopeful finding from this work, Sfanos adds, "is the suggestion that inflammation in the prostate may be a modifiable factor that can be targeted as a means of preventing prostate cancer." ■

"Bipolar" Androgen Therapy (BAT) Trials Under Way

Several years ago, Samuel Denmeade, M.D., Director of the Division of Genitourinary Oncology at the Sidney Kimmel Comprehensive Cancer Center, and colleagues came up with a new concept for treating advanced prostate cancer that seemed counterintuitive: they gave a patient testosterone, lots of it. And then they took it away with androgen deprivation therapy (ADT). And then they gave high-dose testosterone again. And then more ADT.

They called this alternating approach "Bipolar Androgen Therapy" (BAT) because it cycles between polar extremes of very high and very low male hormones. "The idea," Denmeade explains, "is to mess up the cancer cell's ability to adapt." Paradoxically, although low levels of testosterone can make prostate cancer cells grow, "at high doses, the cancer cells don't grow as well, or they die."

"The idea is to mess up the cancer cell's ability to adapt."

Denmeade and colleagues within the Prostate Cancer Research Program are testing BAT in several clinical trials:

The ACROBAT study is testing the rapid cycling of an oral form of testosterone in men whose cancer has just progressed to the castrate-resistant state (CRPC).

The STEP-UP study is evaluating the effectiveness of repeatedly alternating BAT and enzalutamide in men with CRPC cancer who have progressed on abiraterone.

The BATRAD study is testing whether the effectiveness of the bone metastases-targeting drug 223-Radium (Xofigo) can be enhanced when given in combination with BAT. This study is being performed in collaboration with Pedro Isaacsson Velho, M.D., in Porto Alegre, Brazil.

Recently, medical oncologist Mark Markowski, M.D., Ph.D., led the COMBAT study, which tested the effect of BAT in combination with immunotherapy. In another recent study, published in the *Journal of Clinical Investigation*, medical oncologist Laura Sena, M.D., Ph.D., and colleagues demonstrated that BAT has profound effects on the metabolism of CRPC cells. "Based on this work," says Denmeade, "she has developed the innovative APEX clinical trial that combines BAT with DFMO, an oral drug that can block the production of key metabolites required for prostate cancer cell growth and survival." This trial is open for patient accrual.

For more information about these trials, please call 410-614-6337. ■

AI and Your Prostate Cells on a Slide

"Herein lies the future of digital pathology."

Nobody has a crystal ball that will accurately predict exactly what someone's prostate cancer will do – but Hopkins pathologists are working on it.

This crystal ball involves a computer: After a prostate biopsy, the pathologist takes the tissue cores and puts them on a glass slide. The pathologist analyzes them; so does a computer – and "this is revolutionizing the way pathologists diagnose and grade malignancies," says pathologist Tamara Lotan, M.D.

Already, artificial intelligence (AI) and machine-learning algorithms are helping to improve the precision of Gleason grading, to standardize it "and remove human subjectivity from the process." Taking this to the next level, Lotan and pathologist Angelo De Marzo, M.D., Ph.D., are endeavoring to teach AI, and "herein lies the future of digital pathology," she says.

Can AI learn how to identify molecular characteristics in prostate cancer cells more accurately than the human eye, and to predict the patient's course of disease? Lotan and De Marzo believe it can. This year, funded in part by the Prostate Cancer Foundation and private philanthropy, the scientists and colleagues teamed up with AIRA Matrix, a company that uses "deep learning" (involving layers of neural networks).

"We trained deep learning algorithms to identify prostate tumors with two of the most common molecular alterations, *ERG* gene rearrangements, and *PTEN* gene deletions," says Lotan. "By eye, we can't just look at a prostate tumor and tell whether it has these underlying genomic alterations." But with training, "we showed that the computer had excellent accuracy in predicting which tumors had these genetic changes."

Lotan and De Marzo hope this will "pave the way to inexpensive and accessible screening tools," to determine which patients need additional genetic sequencing and to guide precision treatment of advanced cancer. Their work was recently published in *Modern Pathology*. ■

Super-sized, Chemo-Resistant Cancer Cells

Some cancer cells basically thumb their nose at treatment. Other cells may succumb, but not these hardy survivors.

This situation, called cancer therapeutic resistance, is the vexing problem that challenges scientist Sarah Amend, Ph.D. With Ken Pienta, M.D., and colleagues, Amend has been conducting rigorous analysis of the cells that *aren't* killed by chemotherapy.

In recent research, published in the journals *Clinical and Experimental Metastasis* and *Neoplasia*, "we found that the cells that survive cytotoxic chemotherapy enter a unique cell state," says Amend. Normally, all cells undergo cell division by the process of mitosis: a parent cell gives rise to two offspring cells. "We found that while cytotoxic chemotherapy kills cells that undergo mitosis, cells that survive the days and weeks after therapy *exit the typical cell cycle* and progress through multiple growth and DNA replication phases instead – without cell division!" This process, called endocycling, results in jumbo cells, she adds. "The cells are dramatically larger – about 70-fold their normal size."

"The cells are dramatically larger – about 70-fold their normal size."

The investigators discovered that these endocycling cancer cells gain a new power: "They have increased metastatic potential," says Amend. Among other things, "we found that they also have increased directional movement and are highly deformable, thus enabling invasion." Even more concerning is that these endocycling cancer cells "are impervious to subsequent treatment with additional chemotherapy drugs."

However, they may have found a potential Achilles heel: a key protein called Vimentin, the culprit that enables these jumbo cells. "We found that destabilizing Vimentin reverses the motility phenotype." The next step is to figure out how to disrupt this process. "These studies suggest that eliminating this cell state is critical for improving the success of cancer therapy." ■

What do MicroRNAs Have to Do with Inherited Prostate Cancer?

The genes linked to prostate cancer – that we know of — are just the tip of the iceberg. What about the other 98 percent of the genome?

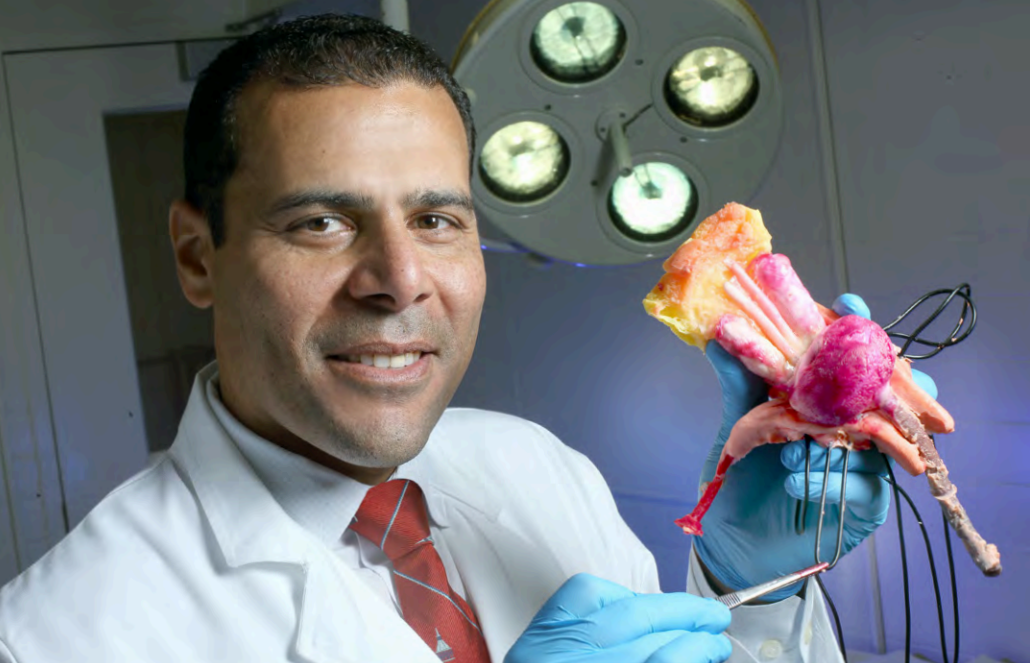
We have learned a lot about certain mutated genes, such as *HOXB13* or *BRCA2*, that can predispose a man to prostate cancer. But guess what? These genes are just the tip of the iceberg.

"They are protein-coding genes," explains scientist Shawn Lupold, Ph.D., the *Catherine Iola and J. Smith Michael Distinguished Professor of Urology* and Co-Director of the Sidney Kimmel Comprehensive Cancer Center Prostate Cancer Program. "They code (provide the information for) cells to make a certain protein or enzyme. And remarkably, less than 2 percent of the genome codes for proteins!"

What about all the genes we don't know much about? The other 98 percent? Some are "noncoding RNAs," tiny throttles, gas pedals, or volume-control knobs. They're "important regulatory molecules that can orchestrate when other genes are turned on or off, or turned up or down," says Lupold. One important class is known as microRNAs, "We are still learning what they do."

In what may be the largest study of its kind, Lupold and scientist William Isaacs, Ph.D., in collaboration with NorthShore University scientist Jenfeng Xu, Ph.D., have sequenced the microRNA-coding region (microRNAome) of 1,500 prostate cancer patients, looking for inherited alterations that are associated with an increased risk of developing lethal prostate cancer.

The results are still preliminary, but they have identified promising genetic variations in several microRNA genes. "We anticipate that these studies may identify new heritable risk factors for prostate cancer that could lead to new diagnostic or prognostic tests." ■



Ghazi: *These models use a remarkable hydrogel that can be made "as soft as fat or as stiff as muscle."*

Déjà Vu: Transforming How Surgery is Practiced and Performed

When he did the actual surgery, Ghazi had a sense of déjà vu: "I've been here before. I recognize what I'm cutting through." He even had muscle memory.

On his computer screen, urologist Ahmed Ghazi, M.B.B.Ch., M.D., is showing a strange video: a radical prostatectomy in double vision. The screen is split, and the operation seems to be shown in duplicate. On both sides of the screen, the robotic scalpel moves, the tissue bleeds, the bleeding is controlled, the prostate is removed, the nerves are spared, and the cancer is gone.

But here is the kicker, the jaw-dropping, "I never would have believed it!" part of the story: the left monitor shows an actual patient's prostatectomy. On the right, the identical procedure is being done on an exact replica of that very prostate. This is not some Hollywood special effects contrivance or computer-generated imagery. It's not virtual reality. Instead, it's a custom 3-D printed and polymer-cast replica of a man's prostate, using his CT scan and designed on 3-D segmentation software. This model was injected with various consistencies of hydrogel to simulate tissue, fat, muscle, blood vessels, and filled with bodily-like fluids. It can bleed.

This is amazing work, and Ghazi, who began developing these models years ago, has brought it to the Brady. The surgical model is so realistic that when looking at the side-by-side pictures on the screen, many surgeons can't tell which is which. It is no exaggeration to say that the implications of this work are mighty, for expert surgeons as well as surgeons in training.

Ghazi, the Brady's new Director of Minimally Invasive and Robotic Surgery, came to Hopkins from the University of Rochester. The first time he used this technology was just before he operated on a 69-year-old man with kidney cancer. The man had a large tumor that took up half of his left kidney and his right kidney was not functioning very well; he also had high blood pressure and was diabetic. If Ghazi couldn't save his kidney, this man would need dialysis.

In preparation, Ghazi attempted the surgery on the pilot model his team had created – and failed. "To tell you the truth, at that point, I felt deflated. I was going to have to go to this patient and tell him that he would need to be on dialysis for the rest of his life." But Ghazi scrutinized the model, dissecting it to see if he could have done something differently. "I realized that there was this sweet spot, where I could remove the entire tumor with negative margins and stay away from those major vessels that were bleeding. I rehearsed the procedure over and over again, up until the night before his surgery."

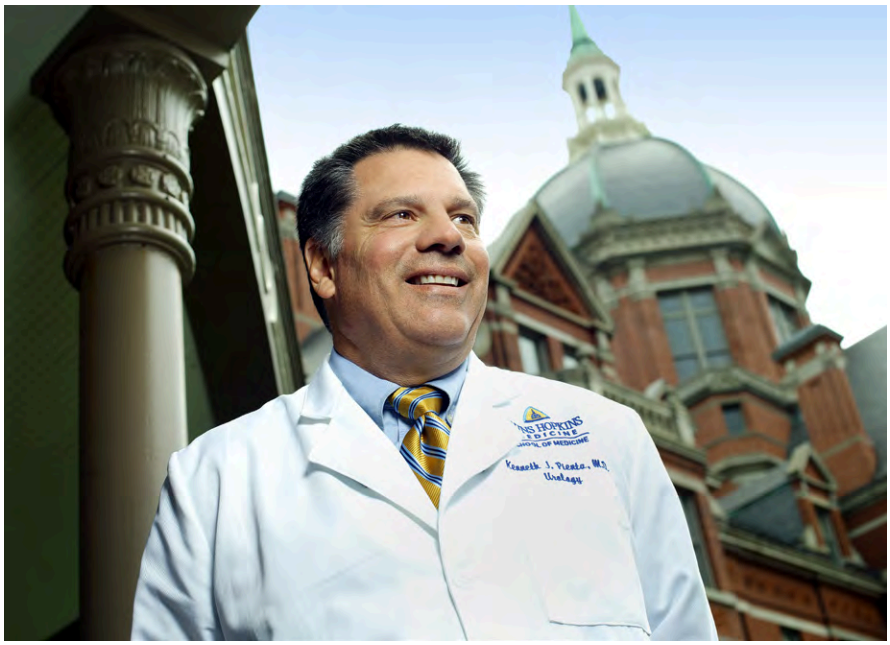
When he did the actual surgery, Ghazi had a sense of déjà vu: "I've been here before. I recognize what I'm cutting through." He even had muscle memory. He performed the surgery in "an almost bloodless surgical plane, where I was able to successfully remove the tumor with negative margins while preserving the rest of the kidney with minimal blood loss, and that was because of the knowledge I got from these rehearsals." More than two years later, the patient is tumor-free, not on dialysis, and back to normal life.

Ghazi has made models for other surgical patients, including men with prostate cancer needing radical prostatectomy. At the Brady, with funding from the Patrick C. Walsh Discovery and Learning Laboratory*, a program within the Surgical Learning and Innovation Center of Excellence (SLICE), Ghazi's models will help surgeons plan and practice operations so they can safely remove cancers, minimize risks, and develop new surgical techniques and procedures.

"Ahmed's work is fascinating because it is next-generation training," says Mohamed Allaf, M.D., "not only for students and residents, but for experienced surgeons. If it's a very difficult operation, we can rehearse it multiple times on these models, and potentially innovate a way to do an operation that might even have been thought to be impossible – have a better result, and make it more safe."

For residents, because the models are so lifelike, they allow for unprecedented practice to learn the procedure and get it right. "While there are computer simulations, those feel more like a video game," says Allaf. "The stakes aren't as high, you don't get the same feel, they don't leak urine, they don't bleed in real time, and blood on a screen doesn't mean as much." Ghazi's work "is already making a difference here. How appropriate that at the Brady, where we pioneered the Urology residency program and training, in Dr. Walsh's 50th year, we are redefining surgical training, with better outcomes and quality of life for our patients."

*Money raised for this project will fund education and research at SLICE. **For more information, please contact bradydevelopment@jhmi.edu or call 410-955-8434.** ■



Pienta: *The revised definition of cancer is this: Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection.*

What is Cancer, Anyway?

This is a serious and age-old question. Kenneth Pienta, M.D., *Donald S. Coffey Professor of Urology,* Director of Research at the Brady, and colleagues are proposing a brand new answer. They recently published their rationale for a new definition of cancer in *Molecular Cancer Research.*

The National Cancer Institute defines cancer as: "*a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body,*" and most definitions of cancer run along these lines.

But there's a problem, Pienta says: "These definitions tend to describe what cancer looks like or does, but do not describe *what cancer is* or *has become*. Current definitions have not kept pace with the understanding that the cancer cell is itself transformed and evolving."

Changing the mindset of what cancer is may change how we treat it.

The revised definition of cancer proposed by Pienta and colleagues is this: Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection. "To the simplest definition of cancer, as a disease of uncontrolled proliferation of cells, our definition adds in the adjective 'transformed' — to capture the many tumorigenic processes that cancer cells adopt to metastasize. Adding "*subject to evolution by natural selection*" modernizes the definition "to include the genetic and epigenetic changes that accumulate within a population of cancer cells that lead to the lethal phenotype."

Pienta and colleagues hope that by changing the mindset, "by understanding that cancer cells are actually following the principles of natural selection, we will help doctors, scientists, and patients better understand how cancer changes over time. This opens opportunities for developing optimal diagnostic and interventional strategies." ■

Inherited Prostate Cancer in Black Men

Previously in *Discovery*, we reported that the first-known prostate-specific cancer susceptibility gene, *HOXB13*, identified in 2012 by Brady scientist William Isaacs, Ph.D., and colleagues – had thrown researchers a curve ball: For a decade, *HOXB13* was thought to pose risk *for men of Nordic European descent only*, because its *G84E* mutation is absent in men of African ancestry.

"X285K is quite possibly the most important marker identified to date for lethal prostate cancer risk in men of African descent."

But then a new mutation was found on this gene: this one, called *X285K*, is linked to aggressive prostate cancer in Black men. As Isaacs states, "*X285K* is quite possibly the most important marker identified to date for lethal prostate cancer risk in men of African descent." This work, funded by donors to the Patrick C. Walsh Hereditary Prostate Cancer Program, was published in the *British Journal of Cancer*.

Now, Brady scientist Jun Luo, Ph.D., the *Alan W. Partin, M.D., Ph.D. Professor of Urology*, is investigating this mutation in new research funded by a grant from the Department of Defense.

X285K, explains Luo, is a "stop-loss" mutation: it alters the gene's molecular machinery and keeps adding amino acids, "totally ignoring the 'stop sign' of its normal cell cycle. When this mutation occurs, *HOXB13* becomes much longer than normal; this stop-loss mutant is also driving prostate cancer growth by affecting other genes."

Think of a mile-long freight train, running amok. There may be ways to stop this train: slow it down, or uncouple some of the cars to make it more manageable. "We are hoping to learn enough to find out its vulnerabilities," says Luo, "and this might lead to gene-targeted precision treatment for prostate cancer patients with this inherited mutation."

Scientists Mayuko Kanayama, Emmanuel Antonarakis, Tamara Lotan, Angelo De Marzo, and Arthur Burnett also contributed to this work. The team is now working with colleagues in Jamaica and Martinique to study the clinical features of patients carrying this mutation. ■

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

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Department of Urology

Amin Herati, M.D.
The Keith L. Bremer Scholar
Department of Urology

Laura Sena, M.D., Ph.D.
The Virginia and Warren Schwerin Scholar
Department of Oncology

Karen Sfanos, Ph.D.
The Beth W. and A. Ross Myers Scholar
Departments of Urology, Oncology, and Pathology

Swaroop Vedula, Ph.D.
The William and Carolyn Stutt Scholar
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Department of Oncology

Read About the Research You Have Helped Make Possible.

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. In fact, some of the major advancements in prostate cancer research were made possible by these gifts.

One huge example is the worldwide adaptation of PSMA-PET imaging. More than 20 years ago, these funds supported physician-scientist Martin Pomper, M.D., Ph.D., who wanted to develop a molecular bloodhound – a small molecule that could track and find PSMA, made by prostate cancer cells, anywhere in the body – and then attach it to a radioactive tracer, so these hidden cells would light up on a PET scan. He did it! Now known as the imaging agent Pylarify, his molecule was developed and is helping patients worldwide.

This Fund owes its existence entirely to patients: patients, who have become partners, make progress happen! 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. This year's awards are hot off the press! We look forward to reporting on these exciting research projects as they unfold.

Remember: ***without you, their work wouldn't be possible!***

New Insights into Mechanisms that Drive Chemotherapy Resistance

This project builds on work discussed on Page 12. Scientist Sarah Amend, Ph.D., and colleagues have discovered that certain cells evolve during cancer treatment and enter an alternative pattern of growth that persists despite chemotherapy: the endocycle. "With this grant, we will define the molecular signature of endocycling cancer cells," she says, "and determine the steps that enable this unconventional way for cancer to grow." ■

Designing a Better 3D-Printer for Patient-Specific Surgical Models

This project builds on work discussed on Page 13. "Imagine the day when urologists can rehearse on an accurate replica of a patient's prostate to optimize the operative approach," says urologist Ahmed Ghazi, M.B.B.Ch., M.D., "maximizing the benefits, reducing the risks, and foreseeing the outcomes of prostatectomy before even making their first incision!"

Ghazi and his team have developed a technique for creating hydrogel organ models from a patient's own scans. These models are made at the Brady's Surgical Learning and Innovation Center of Excellence (SLICE), and are already being used for training.

But as good as they are, the model-making process has room for improvement. "Manufacturing is laborious, expensive, and time-consuming," says Ghazi, "taking up to two weeks." The main reason is that current 3-D printers are a lot better at printing hard things – plastics, for instance – than squishy materials such as Ghazi's hydrogels. Fortunately, the Brady has a secret weapon: our own in-house genius and builder of technology, engineer Dan Stoianovici, Ph.D., and his Urology Robotics Lab. "Dan has designed and built numerous robots and medical devices since 1996, and has the infrastructure and expertise we need."

With this grant, the two labs will collaborate to build *the world's first 3D printer prototype capable of directly printing a hydrogel surgical model.* The implications of this work are exciting, says Ghazi, "extending beyond urology to other medical fields, and potentially to live cell bioprinting and tissue engineering." ■

Working on a New Test for Aggressive Prostate Cancer

Hopkins scientists' studies of molecular biomarkers for aggressive prostate cancer have led to the development of major tests that use blood and urine. But what about semen? The prostate contributes some of the fluid that is in semen, and it makes sense that molecular and genetic changes that are present early on in prostate cancer – maybe before the disease is otherwise detectable – might first be seen in this fluid.

A team of Brady investigators – Amin Herati, M.D., Christian Pavlovich, M.D., and Jun Luo, Ph.D. – is testing a new idea to detect inherited mutations and genomic alterations linked to aggressive and potentially lethal prostate cancer early in the course of the disease, using semen specimens. "If it works," says Pavlovich, "the test will spare many patients the invasive procedures in the traditional biopsy pathway toward prostate cancer diagnosis." The team will enroll 25 patients in this preliminary study. ■

Practice Operating Like an Expert with "Surgical Karaoke"

How do you get to Carnegie Hall? Practice, practice, practice. "The key to achieving true expertise in any skill is simply a matter of practicing, albeit in the correct way, for thousands of hours," says urologist Ahmed Ghazi, M.B.B.Ch., M.D., "Mastery of a surgical technique is far more complex, involving a combination of technical skill, surgical intuition, and long hours of performing procedures. But in the current era of surgery, it has become almost impossible for trainees to accumulate this mastery."

"Any surgical procedure of any expert can be converted using our novel invention."

With co-investigators Swaroop Vedula, Ph.D., from the Whiting School of Engineering, and Ryan P. McMahan, Ph.D., from the Department of Computer Science at the University of Central Florida, Ghazi hopes to give surgical trainees new ways to learn from master surgeons.

Their proposal: "a 'Surgical Karaoke' – coined after the musical karaoke system, but where we track the exact movements from an expert's surgical procedure" and then replay them to trainees using immersive virtual reality technology, for a surgical trainee to replicate the expert's exact movements using hand-controllers. "Any expert surgeon's procedure can be converted using our novel invention." ■

Navigating the Uncharted DNA of Lethal Prostate Cancer

"Imagine having to navigate through a hostile landscape with inadequate intel and using a map that is half empty or missing," says Srinivasan Yegnasubramanian, M.D., Ph.D. "This has been our challenge in understanding lethal prostate cancer: half of its DNA map remains in the dark, hiding potential clues to cure it. But we're about to turn the lights on!"

With co-Principal Investigator Winston Timp, Ph.D., from the Department of Biomedical Engineering, and co-investigators Michael Schatz, Ph.D., from the Departments of Computer Science and Biology, and pathologist Angelo De Marzo, M.D., Ph.D., "We're setting out to fully map the DNA of the deadliest prostate cancers."

Using innovative new technology and computer methods, the team will explore "uncharted genetic and epigenetic territories in lethal prostate cancer, the mysterious expanses of the DNA that have been the most challenging to decipher with previous technologies," Yegnasubramanian says. "We hope to shine a light on

DNA's dark corners – to discover the missing links to understanding why these cancers are so lethal."

They will also be studying the DNA of lethal cancers at the end of life, with deep gratitude for "the courageous spirit of brave men who sadly succumbed to this disease and volunteered to donate their bodies to the fight against prostate cancer. We will study the DNA from the lethal tumors that spread all over their body, and we will stitch together a complete genetic portrait of lethal prostate cancer like never before."

"This isn't just science. It can become our blueprint to conquer prostate cancer."

One more thing the team wants you to know: "This isn't just science. It can become our blueprint to conquer prostate cancer. We aim to better detect, manage, and ultimately defeat this formidable adversary by uncovering its hidden vulnerabilities." ■

BAT: Could Gut Bacteria Make a Difference?

"Bipolar" androgen therapy (BAT) is hormonal therapy of highs and lows for men with castrate-resistant, metastatic prostate cancer (mCRPC): high-dose testosterone, followed by very low levels of male hormones (see Page 11). BAT is promising – but could it be even better? A team of investigators – Laura Sena, M.D., Ph.D., Karen Sfanos, Ph.D., and Tracy Murray Stewart, Ph.D. – hopes to find out.

Their focus is on growth-promoting compounds called polyamines, which may limit the effectiveness of BAT. The agent difluoromethylornithine (DFMO) blocks these polyamines and is being tested in the APEX trial at Hopkins. With this grant, the team will look at the gut microbiome (the population of bacteria in the intestine) in participants of the APEX trial.

The team will study whether "polyamines derived from bacteria living in the gut microbiome can promote therapy resistance to both BAT and DFMO," explains Sfanos. They will characterize the gut bacteria and metabolites (small molecules involved in metabolism), "looking to identify microbiome biomarkers of therapy response and potential strategies to improve this therapy and prolong the lives of patients." ■

Gut Bacteria, Soy, and Fighting Prostate Cancer

For years, scientists have known that prostate cancer doesn't like soy very much. Soy contains isoflavones, which are phytoestrogens, estrogens made by plants. Countries with the highest consumption of soy, as in Asia, have the lowest incidence of prostate cancer. But maybe it's not the soy itself: maybe it's what happens in the guts of people who eat it.

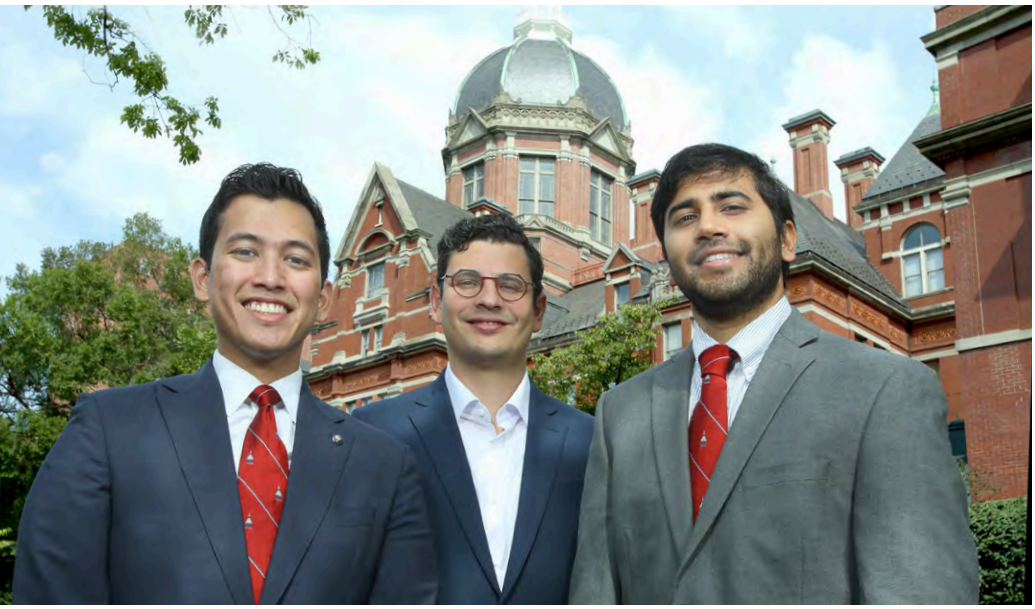
Maybe it's not the soy itself. Maybe it's what happens in the guts of people who eat it.

Scientist Karen Sfanos, Ph.D., is a renowned expert on the microbiome, the population of bacteria, in various parts of the body – such as the intestine. "The microorganisms that reside in the human gut are responsible for converting dietary substances into active compounds that greatly influence human health and disease," she says. In exciting research, "we have discovered that a dietary compound called **equol** – which can *only be made by gut bacteria in some people after they eat soy*, can inhibit the growth of prostate cancer cells."

In the Asian countries with the highest consumption of soy and lowest risk of prostate cancer, there are many people who carry the gut bacteria that produce equol. But wait – there's more! Equol gets even better: "We also found that equol may be a radiosensitizer," Sfanos says. "It may act in combination with radiation therapy to make it more effective in treating advanced prostate cancer." And, because equol is a natural molecule, "it may produce fewer treatment side effects than the traditional androgen deprivation therapy (ADT) that is commonly given with radiation therapy."

Indeed, she continues, equol supplementation in people has been shown to be safe and is already used to improve bone and cardiovascular health, cognitive impairment, dementia, and prostate health. With this grant, Sfanos and colleagues will perform pre-clinical studies in mice using a model of radiation therapy with or without the addition of equol.

"We will study whether equol given in combination with radiotherapy can enhance tumor regression, and we will determine if the immune system plays an important role in the observed response." If the study goes as well as Sfanos hopes, "we hope to obtain the necessary rationale and preliminary data to pursue clinical studies on the use of equol as a radiosensitizer in the treatment of prostate cancer." ■



Alam, Elias, Singla: *Socioeconomic factors and differences in inherited gene mutations contribute to the racial gap in kidney cancer survival.*

DISCOVERY IN KIDNEY CANCER

Active Surveillance in Small Kidney Cancers

In years past, kidney cancer was treated immediately after it was detected. But now we know that not all kidney cancer needs to be treated right away; some small renal masses (SRM; less than 4 cm) may never need treatment. Much of the reassuring evidence about SRM has come from the multicenter Delayed Intervention and Surveillance for Small Renal Mass (DISSRM) registry, established at Hopkins in 2009, and now led by urologic oncologist Nirmish Singla, M.D., M.Sc.

Led by Brady resident Tony Su, M.D., a recent study used data from DISSRM to compare the costs and health outcomes of different treatment options for patients with SRM, including Active Surveillance (AS), partial nephrectomy, radical nephrectomy, and thermal ablation.

"We found that AS is safe and cost-effective in comparison to immediate intervention, and may particularly benefit those harboring very small masses (less than 2 cm)," said Su. This work was published in *The Journal of Urology*. ■

Kidney Cancer and Race

Why are Black patients more likely than White patients to die of kidney cancer? Nirmish Singla, M.D., M.Sc., Director of the Kidney Cancer Program, is leading research efforts to find out more.

In a recent analysis using the National Cancer Database, Brady resident Ridwan Alam, M.D., M.P.H., Singla, and colleagues showed that socioeconomic factors such as educational level, income, neighborhood, occupation, and housing status significantly influence survival. "Targeting these social factors may help close the racial gap in renal cell carcinoma (RCC) survival," says Alam. The team's paper has been published in *Urologic Oncology: Seminars and Original Investigations*.

In another study, medical oncology fellow Roy Elias, M.D., Singla, and colleagues found racial differences in inherited gene mutations among patients with clear cell ccRCC. "We performed comprehensive (whole exome and transcriptome) sequencing on tumors from matched Black and White patients who underwent surgery at Johns Hopkins," Elias says. "In patients of European ancestry, mutations in *VHL* and *PBRM1* were more common. But in patients of African descent, *KMT2C* mutations were more common. These mutations affected how the disease manifested and progressed." Elias presented these results at the 2023 American Society of Clinical Oncology (ASCO) meeting in Chicago.

Notes Singla, the senior author of both studies: "Taken together, our findings may inform prognostic differences among racial groups, help guide personalized therapy, and identify actionable strategies to improve outcomes among patients with RCC."

These investigations were made possible by generous support from Brady Advisory Board member and philanthropist Chad Holliday. ■

Treating Kidney Cancers with Proton Therapy

"The advantage of proton therapy is that it does not exit into normal healthy tissues."

There is no one-size-fits-all therapy for localized kidney cancer. For example, surgery, the mainstay of treatment, is not an option for patients who have other serious medical conditions or complicated tumor presentations. Similarly, stereotactic body radiation therapy (SBRT), which delivers a higher amount of radiation in fewer treatments, may not be optimal for patients with a solitary kidney or large tumors close to nearby organs.

Good news: an alternative approach, proton therapy, is being studied in a clinical trial. Radiation oncologists Sherif Shaaban, M.B.B.Ch., M.Sc., and Curtiland Deville, M.D., at the Johns Hopkins Proton Therapy Center at Sibley Memorial Hospital's Kimmel Cancer Center, have received a grant from the Robert L. Sloan Fund for Cancer Research, for a prospective Phase I/II study, along with Brady co-investigators Nirmish Singla, M.D., M.Sc., Armine Smith, M.D., and Justin Benabdallah, M.D.

"Proton therapy uses a beam of protons to deliver radiation directly to the tumor," says Shaaban. "The advantage of proton therapy is that it does not exit into normal healthy tissues. We can control where the proton releases the bulk of its cancer-fighting energy – causing the most damage to the tumor cells – while sparing healthy tissues and organs." Shaaban also has been selected to develop the protocol for this at the ASCO/AACR Methods in Clinical Cancer Research Workshop. ■

Who Will Benefit from Immunotherapy for Metastatic ccRCC?

Important clues can be found in routine pathology slides.

Immunotherapy drugs called "checkpoint inhibitors" have revolutionized treatment for patients with metastatic clear cell renal carcinoma (ccRCC), the most common type of kidney cancer. But they don't work equally well in all patients. Which patients will benefit the most?

Hopkins scientists have found predictive clues in a recent study of routine pathology slides of patients' cancer biopsies. Led by pathologist Julie Deutsch, M.D., the investigators studied three groups of patients with metastatic ccRCC who received checkpoint inhibitors (specifically, anti-PD-1-based drugs). They looked for the presence of immune cells in the tumors (known as tumor-infiltrating immune cells), and dead cancer cells (necrosis).

"We found that patients whose biopsies showed the presence of tumor-infiltrating immune cells and the absence of necrosis had improved survival," says Deutsch. "This predictive ability was further refined when adding in the presence of a common kidney cancer mutation, called *PBRM1*." These findings "will help us in selecting patients for immunotherapy," says urologic oncologist Nirmish Singla, M.D., M.Sc., who took part in the study.

When the investigators searched the literature looking for biomarkers linked to the success of immunotherapy in these patients, they found limited evidence incorporating pathology slides. "Our findings demonstrate the important information that can be obtained from these slides, and provide support for including slide analysis in biomarker studies." Their findings were published in *Cell Reports Medicine*. ■

In-Depth Study of ccRCC Yields New Insights

In a series of elegant studies, pathology scientists Hui Zhang, Ph.D., M.S., and T. Mamie Lih, Ph.D., together with investigators from the Clinical Proteomic Tumor Analysis Consortium (CPTAC), have discovered several new ways of characterizing clear cell renal cell carcinoma (ccRCC).

How do you approach a very complex form of cancer? With a comprehensive and in-depth plan of attack, using multiple analytic techniques. In a recent study published in *Cancer Cell*, Zhang's group integrated histopathologic, proteogenomic, and metabolomic analyses of samples from 213 patients to craft a thorough profile of ccRCC. "We found heterogeneity (many different types of cells) within ccRCC tumors, along with histological signatures of aggressive forms of disease," says Zhang. They also discovered some promising candidate biomarkers for prognosis, and this work may one day lead to new ways to treat ccRCC.

In another study, published in *Cell Reports*, the scientists looked at molecular dysregulations of proteins called glycoproteins in the tumors of more than 100 patients with ccRCC. They found certain patterns and signaling pathways that carry prognostic value in ccRCC – and these, too, may have a role in the development of new strategies for treating this disease. "These studies provide a valuable resource for future translational research in kidney cancer," says Zhang. ■

Treating High-Risk Kidney Cancer Before it Spreads

Is it a question of timing? Should we try the drug even earlier?

"When cancer is localized within the kidney, nephrectomy (kidney removal) is the treatment of choice," says Mohamad Allaf, M.D. However, surgery alone is not enough for all patients diagnosed with localized kidney cancer. In about one-third of patients, cancer comes back and spreads beyond the kidney.

Allaf is hoping to change this statistic by hitting the cancer even harder at the beginning. "Drugs called immune checkpoint inhibitors (ICI) have improved the outcomes of patients with metastatic kidney cancer," he says. "What if we gave these ICIs to patients around the time of surgery – when the disease is still localized – to help decrease their chances of recurrence?"

Allaf recently led the multi-center phase III PROSPER RCC trial, in which nearly 900 patients with RCC were randomly assigned either to receive the ICI drug nivolumab or no drug at the time of nephrectomy. "Unfortunately, this trial found no benefit in giving nivolumab in this setting – but fortunately, this was the first phase III ICI trial of its kind in RCC."

In other words, it was a start, and we can learn from it. Allaf and colleagues collected "droves of biological specimens and data" from this trial. Then they and others wondered: Is it a question of timing? Should we try the drug even earlier?

And so they did. Allaf then led the first prospective trial of nivolumab before surgery for patients with high-risk localized RCC – cancer that is likely to come back and to spread – at Johns Hopkins. "We showed that nephrectomy after nivolumab is safe and feasible."

Nirmish Singla, M.D., M.Sc., recently analyzed blood and tissue samples acquired from this phase I trial. He found important relationships between immune cells within the tumor microenvironment and response to ICI. "We also found changes within the primary tumor and in the circulation that were induced by nivolumab treatment, and these provide support for more perioperative (before surgery) ICI approaches in the future, perhaps in combination with other ICI drugs."

Allaf presented the clinical results from the PROSPER RCC trial at the 2022 European Society for Medical Oncology (ESMO) Congress in Paris, and Singla then presented the correlative results from the phase I trial at the 2023 American Urological Association (AUA) Annual Meeting in Chicago. Singla also serves as the Principal Investigator of a translational research grant awarded by the Department of Defense to further study the effects of ICI on primary tumors in RCC. ■

Smith: *Radical cystectomy profoundly affects quality of life. Is there a better way? Organ-sparing procedures now being tested at Hopkins could dramatically improve life after surgery.*

DISCOVERY IN BLADDER CANCER

New Clues to Treating Two Forms of Bladder Cancer

Small cell/neuroendocrine bladder cancers (SCBCs) are rare, highly aggressive, and difficult to treat. But in a recent study, published in *European Urology*, Brady scientist Woonyoung Choi, Ph.D., and colleagues have gained insights that may lead to new ways to treat these lethal cancers.

"We defined three molecular subtypes of SCBC that resemble well-characterized subtypes in small cell lung cancer," says Choi. Among these subtypes, some markers and immune signatures suggest the cancer may be vulnerable to an immune checkpoint-inhibitor (ICI) drug, and some "contained distinct targets for clinically available antibody-drug conjugates."

Non-Muscle Invasive Bladder Cancer (NMIBC) that does not respond to BCG: For patients with non-muscle invasive bladder cancer (NMIBC), the first line of treatment is Bacillus Calmette-Guerin (BCG), a form of immunotherapy given directly within the bladder. If that does not work, the next step is intravesical chemotherapy, a combination of the drugs gemcitabine and docetaxel (GEMDOCE). In another study, Choi, urologist Max Kates, M.D., and Brady colleagues looked for gene signatures that can help predict who will be likely to respond to GEMDOCE treatment, and who will likely be cured by it. They performed whole transcriptome RNA sequencing and DNA panel sequencing on a cohort of patients with BCG-unresponsive NMIBC who underwent intravesical GEMDOCE, looked for gene signatures that were linked to success of treatment – and found some. The next step will be to validate these findings in larger studies. ■

Improving Quality of Life After Radical Cystectomy

Do all those organs need to come out?

Radical cystectomy is a tough operation. It's not just removal of the bladder: in men, it includes removing the prostate and seminal vesicles, and in women, it includes removing the anterior vaginal wall, ovaries, uterus, fallopian tubes and urethra.

"This surgery profoundly alters the anatomy and functionality of the genito-urinary system," says Armine Smith, M.D., Director of Urologic Oncology at Sibley Memorial Hospital. "It causes sexual dysfunction in a large number of men and women, and urinary incontinence in those who choose to have an orthotopic replacement of their native bladder."

Do all those organs need to come out? Investigators at the Brady and the Johns Hopkins Greenberg Bladder Cancer Institute are studying organ preservation during cystectomy. The hope, says Smith, "is to dramatically improve quality of life after surgery for both men and women."

In a prospective, randomized-controlled study, Smith, with urologists Max Kates, M.D., and Sunil Patel, M.D., will look at preserving the prostate in men with bladder cancer who need radical cystectomy. The research, Smith says, "will show the extent of the benefit of this surgical modification and allow us to answer the question of who is the best candidate for this type of surgery."

There is an organ-sparing radical cystectomy for women, as well. "It is a modified surgical technique that preserves some or all gynecologic organs and the urethra," says Smith. "Preserving these structures improves pelvic support, the endocrine milieu, and sexual function by maintaining vaginal anatomy and minimizing disruption of nerve pathways – but organ and nerve preservation in women is even less studied than in men!"

Smith, who also leads the Women's Bladder Cancer Program, is taking a multifaceted approach to improving this operation for women. It includes:

- creating MRI-guided functional maps of the pelvis to allow better nerve preservation during cystectomy, "in collaboration with the pioneers of multiparametric pelvic MRI at the National Cancer Institute, Baris Turkbey, M.D., and Peter Choyke, M.D.," and
- designing 3D training models to improve surgical techniques and organ preservation (with Brady urologist Ahmed Ghazi, M.B.B.Ch., M.D.).

"These innovations may revolutionize how we care for women with bladder cancer." ■

Patients Talked; We Listened, Studied, and Came Up with a Plan to Make it Better. Now We Want to Test it.

Every facet of ERAS targets factors of delayed recovery, such as slow return of bowel and urinary function, immobility, and pain.

Transurethral resection of a bladder tumor (TURBT), an outpatient procedure, "is often described as an 'incision-free' and 'well-tolerated' operation," says urologist Max Kates, M.D., Director of Urologic Oncology at the Brady. But the people doing the describing generally are not the people who actually experience TURBT. In fact, "many patients experience significant distress and discomfort with the procedure."

Earlier in 2023, Kates led a multicenter prospective study to characterize recovery and define the toxicity, or side effects,

of ambulatory TURBT. "The main post-operative problems for patients included dysuria (painful or uncomfortable urination), penile or vaginal pain, suprapubic pain, and urinary urgency and frequency," Kates says. The study's participants included 159 patients with a median age of 72 years who had undergone two prior TURBTs. About 48 percent reported dysuria, 44 percent reported penile pain, and 22 percent reported vaginal pain. Patients with a higher body mass index reported worse dysuria, and patients with diabetes were more likely to experience suprapubic pain. Other problems included urinary urgency and frequency; constipation; and lack of sleep; 10 percent of patients reported an urgent clinic or Emergency Department visit, and about 7 percent had to be admitted to the hospital.

The study's findings confirmed what Kates and colleagues already knew: "The amount of distress and discomfort experienced by some patients after TURBT is underappreciated." The investigators are determined to do something about it. "We want to improve the TURBT experience," says Kates.

What is ERAS?

At Hopkins, more than 4,000 surgical patients each year are benefiting from a protocol called Enhanced Recovery After Surgery (ERAS). Every facet of ERAS targets factors of delayed recovery, such as slow return of bowel and urinary function, immobility, and pain. So far, ERAS has worked well in more than 20 colorectal and gynecological procedures.

A Brady team led by Kates believes ERAS can help TURBT patients, too. After doing some more listening – to patients as well as doctors – the team came up with TURBT-specific perioperative improvements (implemented immediately before, during, and in the recovery period after surgery). "We developed our ERAS protocol based on feedback from 159 patients who responded to surveys, input from a convened panel of bladder cancer patients, and guidance from a group of clinicians who care for these patients."

This fall at Hopkins, to evaluate the effectiveness of this TURBT-specific ERAS protocol compared to usual care, Kates and colleagues will conduct the Enhancing Bladder Cancer Care (EMBRACE) Randomized Controlled Trial. "We will enroll 100 patients with suspected or known bladder cancer, age 18 and over, who are undergoing initial or repeat ambulatory TURBT," he says. "We hypothesize that patients exposed to the ERAS protocol will experience higher quality of recovery after ambulatory TURBT compared to those receiving usual care." ■

A New Bladder Cancer Drug, and an Odd Link to Improvement

Patients who experienced any type of skin toxicity were more likely to benefit from EV treatment than those who did not.

A team led by Hopkins oncologist Jean Hoffman-Censits, M.D., recently made an unusual discovery. It has to do with a drug called enfortumab vedotin (EV), which is in a novel class of chemotherapy agents called antibody-drug conjugates (ADC).

"Unlike traditional chemotherapy, ADCs circulate in the bloodstream until the antibody portion finds its target on cancer cells, and then it releases the drug directly into the cancer environment," says Hoffman-Censits. "EV is a powerful tool for use in bladder cancer – particularly as it is effective against the most aggressive forms."

In a retrospective study, the team analyzed data from Hopkins patients treated with more than one dose of EV. Of 56 patients, about 48 percent had some degree of skin toxicity (a range of symptoms ranging from mild rash and itching to blisters and peeling).

In this study, unexpectedly, skin side effects turned out to be a plus! "Our group noted that patients who experienced any type of skin toxicity were more likely to have improvement in their cancer from EV treatment than those who did not," Hoffman-Censits says. This work was published in *European Urology Open Science*, and "we are working to validate these findings in a larger study and to elucidate mechanisms of this effect." ■

Urine "Liquid Biopsies" for Bladder Cancer

"Our current methods to detect the presence of bladder and upper tract urothelial cancers are suboptimal," says David McConkey, Ph.D., Director of the Johns Hopkins Greenberg Bladder Cancer Institute. "Cystoscopy remains the gold standard for diagnosis and surveillance, but it is expensive and painful for some patients."

There is no definitive "liquid biopsy," looking at urothelial cells shed in the urine, for bladder cancer, but McConkey and colleagues are studying several promising approaches.

With collaborators in the Southwest Oncology Group (SWOG), the Department of Urology at MD Anderson Cancer Center, and industry collaborators, McConkey has been leading efforts to use urine liquid biopsies to predict and track benefit from intravesical interferon gene therapy (with Adstiladrin) and the immune checkpoint inhibitor, atezolizumab (Tecentriq). McConkey, with coinvestigators Joshua Meeks, M.D., Ph.D., (Northwestern University) and Robert Svatek, M.D., (UT San Antonio), has competed successfully for $500,000 from the National Cancer Institute's Biomarkers, Imaging, and Quality of Life Studies Funding Program. With this award, they will perform liquid biopsy measurements on pre- and post-treatment urine samples collected in SWOG's S1602 PRIME trial, which enrolled 1,000 patients and compared the effects of two different strains of BCG.

Their efforts will help Brady investigators Max Kates, M.D., and Noah Hahn, M.D., and their collaborators in the international ECOG-ACRIN research group. "They are working to integrate urine liquid biopsies into their ongoing Phase-3 EA8212 BRIDGE trial," says McConkey, "comparing clinical outcomes in patients randomized to receive either BCG or gemcitabine plus docetaxel in the frontline setting." ■

IN MEMORIAM:
Alan W. Partin, M.D., Ph.D.

"Alan was consistently at the heart of discovery and innovation in the field of urology."

With great sadness, we report the passing of urologist Alan Partin, M.D., Ph.D., who succumbed to glioblastoma at the age of 62. Partin retired last year as Urologist-in-Chief of the Johns Hopkins Hospital and *Jakurski Family Director* of the Brady.

"Throughout his career as a clinician, scientist, and teacher, Alan was consistently at the heart of discovery and innovation in the field of urology," says Mohamad Allaf, M.D., who succeeded Partin in 2022.

Partin came to Hopkins in 1982 after a stellar college career at the University of Mississippi. At Ole Miss, he double-majored in chemistry and mathematics, was the Valedictorian of his graduating class, played football all four years, and was named an Academic All-American football player. At Hopkins, Partin earned his M.D. and his Ph.D. in Pharmacology; during this time, he met Donald Coffey, Ph.D., the Brady's Director of Research. Coffey became Partin's research mentor and lifelong friend.

During Partin's last year of medical school, he worked with Patrick Walsh, M.D., and discussed the possibility of applying for training in Urology, and Walsh suggested that he "shadow" him in his clinics. While seeing patients and discussing prostate cancer staging, Partin asked Walsh a question: "In prostate cancer, is it possible that tumor volume – rather than percent of the gland involved – would be a more accurate way to estimate tumor aggressiveness? Which is worse, a ping-pong ball inside a watermelon, or a ping-pong ball inside of a tennis ball?" Walsh, Partin later wrote, "agreed that this was a terrific question," and they carried out a study to find out. "It turned out that the percentage of the gland involved (more or less than 5 percent) was more accurate in predicting curability than tumor volume," Partin said. This turned out to be the first of many clinical projects that Partin would work on with Walsh, some of which are the most cited papers in the field.

Partin was accepted for the Brady residency, where he learned meticulous surgical techniques and continued his research. The most referenced and clinically useful discovery of his career was the nomogram now known as the Partin Tables. In 1993, based on Walsh's detailed database of his first thousand patients, Partin was able to make a pre-operative estimate of the pathologic findings at radical prostatectomy. His calculation used three simple parameters: the PSA value, the findings on rectal examination (the clinical stage), and the Gleason score on the biopsy.

"With the Partin Tables, suddenly there was an algorithm that allowed patients and physicians to predict the probability that the cancer could be cured."

"Before this discovery, it was difficult to know who might benefit most from surgery," says Walsh, "because there was no accurate means to determine curability. However, with the Partin Tables, suddenly there was an algorithm that allowed patients and physicians to predict the probability that the cancer could be cured." One noted medical oncologist termed the Partin Tables the "prognostic paradigm of the 1990s," and for decades, the Partin Tables have helped patients and doctors worldwide estimate the prognosis for men with newly diagnosed prostate cancer.

In later work, Partin and his lab helped to develop several innovative tests to identify and track prostate cancer, including the Prostate Health Index (PHI) test.

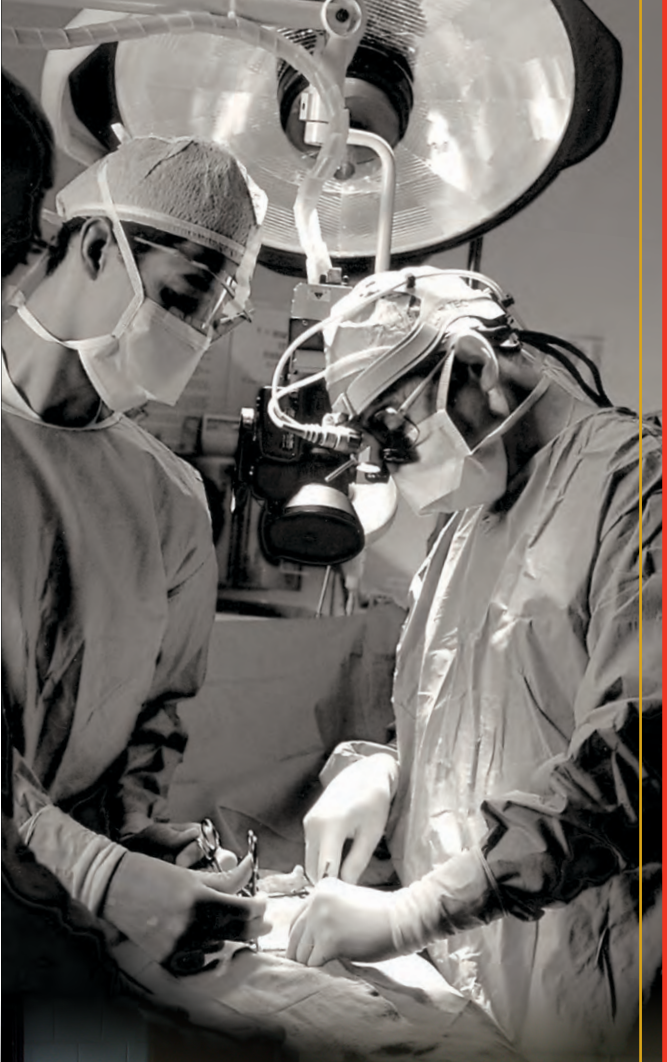
After finishing residency, Partin joined the Brady faculty as an associate professor, was shortly promoted to full professor, and was honored with an endowed chair, the *Bernard L. Schwartz Distinguished Professorship in Urologic Oncology*. In 2004, he succeeded Walsh as the Brady's fourth Director.

Under his leadership, the Brady doubled its research space and enjoyed significant expansion with projects such as the Greenberg Bladder Cancer Institute and new clinical space at Green Spring Station Pavilion III.

Partin contributed to more than 600 scientific articles, publications, and presentations. He served as editor of the respected journal *Urology* for a decade and was the recipient of many honors, including the British Association of Urological Surgeons' distinguished St. Paul's Medal; the American Urologic Association's prestigious Gold Cystoscope and Distinguished Service Awards; the Ambrose Monell Research Award; the David Koch Prostate Cancer Research Award; and the Merck Young Investigator Award. He also was elected to the American Association of Genitourinary Surgeons, the world's most distinguished urologic organization.

"Alan was a mentor, adviser, and dear friend to many of us here at the Brady and throughout the field," says Allaf. "He is deeply missed." Partin is survived by his wife, Vicky, their four sons and their wives, and five grandchildren, and by his brother and sister-in-law.

In 2022, with contributions from patients, friends, and family, the *Alan W. Partin, M.D., Ph.D., Professorship in Urology* was established to support a faculty member's research to develop diagnostic tools and new treatments for prostate cancer. ■



Join us in honoring Dr. Patrick C. Walsh on his 50th anniversary at the Brady Urological Institute by making a gift to establish the **Patrick C. Walsh Discovery and Learning Laboratory at the Surgical Learning and Innovation Center of Excellence (SLICE)**, the Brady's future home of transformative surgical discovery, innovation, and learning.

The Walsh Discovery and Learning Laboratory will incubate new discoveries and nurture urologic surgeons, inspired by Dr. Walsh's steadfast dedication to the healing and well-being of every patient.

Discovering 50 Tomorrow

CELEBRATING DR. PATRICK WALSH

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