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DISCOVERY

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Tamara Lotan
Pathologist, Educator, Scientist
Our New Director of Research

BIG PLANS FOR BRADY RESEARCH

INSIDE THIS ISSUE

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I hope that one day soon, patients from all over the world will be able to gain insights and make better health decisions based on our data.

FULL SPEED AHEAD

Even amid today's challenging funding environment, the Brady continues to thrive.

We are making robust advances in treatment and expanding our research mission in basic science, translational science, and technology. Our clinical trials program has grown tremendously: three years ago, the Department of Urology was running six clinical trials with two full-time staff. Today, we have a portfolio of 40 clinical trials, and our team managing this effort has tripled in size. Thanks to two generous gifts, we are now able to enhance our clinical trial offerings at our Sibley Memorial Hospital site in Washington, D.C.

We are investing in Artificial Intelligence (AI). Our new Division of Quantitative Science is co-led by bioinformatician Eddie Imada and urologist Arun Rai. With other Brady investigators, they will be using computational biology and AI to leverage our unrivaled, massive repository of patient data and biospecimens to answer a multitude of important questions. Many questions will come from our scientists and clinicians, who are always seeking new insights that will help our patients. But I hope that one day soon, patients from all over the world will also be able to gain insights and make better health decisions based on our data.

True to the mission of the Patrick C. Walsh Prostate Cancer Research Fund, we continue to invest in innovative quests for discovery. Nine research projects were recently awarded seed money from this fund, allowing scientists to test bold ideas that are poised to make the next breakthrough in the way we detect, treat, and understand prostate cancer. A personalized prostate biopsy robotic system, developed by Dan Stoianovici and Misop Han using these funds, was recently awarded a coveted National Institutes of Health R01 grant and continues the legacy of technology developed in our URobotics Laboratory.

I am thrilled to feature our new Director of Research, Tamara Lotan, on the cover of this edition of *Discovery*. Longtime readers have seen her name featured numerous times. She is a urologic pathologist, a prolific, world-renowned scientist and a dedicated teacher and mentor, particularly for students in our Schaufeld Program, which she co-leads with me.

The Brady has so much to be proud of – including our faculty, staff, residents, and fellows. Together, with our patients and generous supporters, we are partners in discovery and innovation. I hope you enjoy the pages that follow, because the Brady is an amazing place!

MOHAMMAD E. ALLAF, M.D.
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ON THE COVER *Tamara Lotan, M.D., the Brady's new Director of Research. She is the first pathologist and the first woman to hold this position, and an internationally renowned physician-scientist.*

COVER STORY

BIG PLANS FOR BRADY RESEARCH

Tamara Lotan, M.D., the *Rose-Lee and Keith Reinhard Professor of Urologic Pathology*, is the Brady's new Director of Research. She is the first pathologist and the first woman to hold this position, and only the sixth research director in the Brady's history.

An internationally renowned physician-scientist in the field of urologic pathology and the co-author of more than 200 scholarly publications, Lotan is also Co-Director of the Schaufeld Program for Prostate Cancer in Black Men, with Urologist-in-Chief Mohammad Allaf, M.D., the *Jakurski Family Director,* and is a dedicated mentor of the program's Schaufeld Scholars.

Lotan is the operational definition of someone who wears many hats, all of them well. Having a non-urologist as the Brady's Research Director may be unconventional, says Allaf, but it's not unprecedented; Kenneth Pienta, M.D., the *Donald S. Coffey Professor of Urology*, her predecessor (see page 9), is a medical oncologist. "The Brady's forward-thinking approach looks for answers through team science and multidisciplinary work – we see beyond just urology. The diseases we treat bridge urology, pathology, medical oncology, radiation oncology, basic and clinical science, and data science."

Allaf and Lotan have big plans for Brady research. "My goal is to elevate and support a number of flagship research programs," says Lotan, "and within each one, to have a partnership between clinical researchers and translational researchers, and then the third leg of the triad is data scientists. Large data sets are critical to facilitating new discoveries in research."

SO MUCH DATA

The Brady has an unrivaled trove of patient data – blood, tissue, and urine samples; genetic test results; and imaging scans – available for study down to the molecular level. "Urologic pathology really started at Hopkins, and grew along with Patrick Walsh, M.D., in a program where he transformed the radical prostatectomy. More than 30,000 prostatectomies have been performed at the Brady – an enormous scale unmatched by most other institutions. In addition to tissue, a large number of these prostatectomy patients have detailed information about their clinical outcomes after surgery," many of them collected over decades.

WHAT CAN BE LEARNED FROM THIS DATA? SO MANY THINGS!

For example: **Patient A is 58, with a family history of prostate cancer.** His father had a radical prostatectomy at the Brady 30 years ago, performed by Walsh. His father's initial PSA test, plus years of follow-up PSA tests, his initial biopsy slides, a CT scan, and prostatectomy specimen are stored at the Brady. Patient A was diagnosed with localized prostate cancer, Gleason 8. His biopsy slides and tissue samples from the robotic prostatectomy performed by Allaf are also at the Brady, plus his prostate MRI.

Patient B, age 74, was diagnosed with metastatic, Gleason 9 prostate cancer and is being treated by medical oncologist Sam Denmeade, M.D. Four years ago, William Isaacs, Ph.D., did a complete analysis of his *germline* DNA and found a mutated *BRCA2* gene. Using biopsies of tumors from metastatic sites, Lotan and others have conducted analysis of the *somatic* DNA changes – alterations in the tumor that happened as his cancer evolved – and cataloged many epigenetic changes that helped drive his cancer to become more aggressive. The cancer in these sites was different from that sampled in his original prostate biopsy. Patient B also underwent a PSMA-PET scan as part of a clinical trial, and has had a prostate MRI, a CT scan, and a nuclear medicine bone scan.

Patient C has Gleason 6 prostate cancer, and is being closely followed in the Active Surveillance Program by his urologist, Christian Pavlovich, M.D. He has had three prostate biopsies, four prostate MRIs, and six PSA tests, as well as *germline* testing.

Alone, each of these patients has innumerable data points that may yield clues to how prostate cancer develops, spreads, or simply percolates within the prostate. Combining clinical data with the rich data stored in the pathology and radiology images will yield even more information. Multiply that by the many thousands of Brady patients – over the spectrum of urologic diseases, *malignant and benign* – and it's too much for any individual scientist to begin to mine.

Allaf and Lotan: *Seeking answers in the Brady's unrivaled trove of patient data to help patients at every stage of disease.*

"We need artificial intelligence (AI) and deep (machine) learning," says Lotan, "to integrate the big clinical data with the pathology and radiology imaging data – which is *billions of pixels on many thousands of slides and images* – times all of those patients. There are research platforms that will generate more data on those histologic images, the genomic data from the pathologic specimens or from the germline DNA of the patients. We can layer on to that by interrogating the proteins and immune cells we see in the tumor microenvironment. With newer spatial technologies, we can even look at the DNA alterations within individual cells in relation to their neighbors. Start with 30,000 patients, if we created detailed maps of all those tumors at the protein level, each one would have *trillions of data points*. AI, or deep learning, can then be leveraged to learn from these – better predicting which patients have aggressive tumors or are likely to respond to a particular therapy. Then, can we further identify these patients while their tumors are still localized to the prostate, or maybe before they even develop cancer?"

Continued on the next page >

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There are millions more data points from Brady bladder cancer, kidney cancer and testicular cancer patients. Millions of patient data points from benign diseases; for example, Walsh has kept a registry of patients with hereditary benign prostatic hyperplasia (BPH) for decades. Millions of patient data points from pediatric urology patients, and from female urology patients.

And yet: Lotan is quick to note that "All of this is only as good as the questions we're asking." To help ask and answer these questions, Lotan is working closely with urologist Arun Rai, M.D., M.B.A., M.S., who is the Brady's new Clinical Director for the Division of Quantitative Science. "In terms of the questions we're asking, they will be clustered in disease-specific programs, levering a multidisciplinary approach."

In bladder cancer alone, there are several research working groups, says Lotan. One centers around liquid biopsy, looking at circulating DNA in urine and in the blood, to predict which cancers are likely to progress. "Another group is studying organ preservation, similar to focal therapy in prostate cancer. They also have their own AI and digital pathology program. We have to do a lot of work to digitize all the images of the tumors across various tumor types, to use AI to identify underlying molecular alterations – and hopefully discover biomarkers to predict progression, further fueling our multidisciplinary clinical research programs."

Lotan is excited about the Brady's Division of Quantitative Science, "which was established with a donation from a generous philanthropist about a year ago." Newly hired bioinformatician Eddie Imada, Ph.D., an expert on computational genomics, will help make possible "a lot of our digital pathology efforts, our genomics efforts, and then some of the AI efforts with the goal of supporting Dr. Rai to develop tools that patients can use to predict their risk of developing cancer, or their risk of recurrence. They can ask questions of *our* data using their own data, and interrogate it by an AI algorithm" (see Dr. Allaf's letter). "Before we can do that, we are busy updating all of the clinical databases, genomics databases, and modernizing everything – so we don't have to manually go into the clinical record, which dates back to Dr. Walsh's early patients."

In addition to overseeing research and conducting active research herself, Lotan and a team of urologic pathologists see about 8,000 consultations a year from men around the world who seek second opinions on their prostate biopsies. "We have a very active consensus conference," she says. "We meet every day to talk about difficult cases. Frequently we make some really significant changes that alter clinical management of the patient's tumor," either upgrading, when a man's prostate cancer is more aggressive than originally thought, or occasionally downgrading, when abnormal benign cells are misdiagnosed as cancerous.

Of all her many roles, co-directing the Schaufeld Program is perhaps closest to her heart. Lotan helps place scholars – recent college graduates who are interested in biomedical careers – in research labs throughout Hopkins Medicine, spends time mentoring them, and sets up numerous mentorship, educational, and professional development opportunities for them.

The program is growing, Lotan says. "We have an additional Schaufeld scholar; we had six, and we are moving to seven. We've had five scholars graduate, and four have already matriculated to medical school!" ■

Lotan with Schaufeld Scholars: *So far, four Scholars have graduated and are now in medical school.*

USING AI TO STANDARDIZE PROSTATE CANCER GRADING

Lotan's team is working to develop AI algorithms that can predict lethal prostate cancer after prostatectomy independent of grading, perhaps even at the time of biopsy.

"Digital pathology is revolutionizing the way that pathologists assess prostate tumors, and making it possible to use histopathology-based AI algorithms to improve pathologic diagnosis and grading," says pathologist Tamara Lotan, M.D.

These computer algorithms learn from human pathologists' notes and from patients' clinical outcomes, then make predictions about how aggressive prostate tumors may be. In a project sponsored by the Prostate Cancer Foundation, Lotan's team has been working with an Indian pathology AI company called AIRA Matrix to move histopathology AI tools into routine clinical use.

"Gleason grading can be subjective," Lotan notes, "since it involves a pathologist looking at patterns of prostate cancer cells and determining which type is the most common, and which type is the second most common. There is room for error."

In a recent study published in *European Urology Oncology*, Lotan's team compared traditional visual Gleason grading and AI-based grading for predicting metastases after prostatectomy. Their study found that AI grading is already indistinguishable from human pathologist grading in doing this. "AI grading could make specialist grading available at centers that lack dedicated urologic pathologists."

Now, Lotan's team is working to develop AI algorithms that can predict lethal prostate cancer after prostatectomy independent of grading, perhaps even at the time of biopsy. In a manuscript recently accepted by *European Urology*, Lotan's team showed that their algorithms can be trained to directly predict risk of lethal prostate cancer from diagnostic pathology images, and can use biopsy samples to help determine cancer risk. The team validated these findings in a larger patient population with collaborators at Harvard University. ■

Walsh and Singla: *Walsh, Discovery's founding Editor-in-Chief, and Singla, who carries on his legacy.*

Singla Takes the Helm of *Discovery*

"I think Discovery's *name is very fitting. It is the legacy that Dr. Walsh championed and embodies the core research mission of the Brady: making new discoveries to advance the field and improve the lives of patients."*

Discovery has a new Editor-in-Chief: Nirmish Singla, M.D., M.Sc. He is the second to hold this position, after Patrick C. Walsh, M.D.

"I am stepping down after more than 25 years," says Walsh, *Discovery's* founding Editor-in-Chief, "and am thrilled that Nirmish has accepted this position. He was selected because of his scholarship, depth of knowledge in all areas of urologic oncology, and dedication to excellence. In addition to being an outstanding surgeon and clinician, he wears many hats: Director of Translational Research in Genitourinary Oncology, Director of the Kidney Cancer Program, Co-Director of the Upper Tract Urothelial Cancer (UTUC) Program, and Vice Chair and Physician Advisor for Quality, Safety & Service at the Brady. I look forward to his many future years of leadership."

Singla earned his B.S.E in Biomedical Engineering from the University of Michigan, and his M.D. from the University of Michigan Medical School. He completed his residency in Urologic Surgery at the University of Texas Southwestern (UTSW) Medical Center, and spent an extra year there as a postdoctoral research fellow in urologic oncology, with a specialized focus on translational research in kidney cancer. During this time, he also earned a Master of Science in Clinical Science degree through the Center for Translational Medicine at UTSW. He then completed an advanced surgical fellowship in urologic oncology at Memorial Sloan Kettering Cancer Center in New York.

When he joined the Brady in 2020, Singla hit the ground running: conducting clinical and translational research, teaching residents and fellows, and caring for patients. The lead principal investigator on multiple federal research grants and co-author of more than 300 articles and textbook chapters, he has established an international reputation as a leader in urologic oncology.

"I think *Discovery's* name is very fitting," says Singla. "It is the legacy that Dr. Walsh championed and embodies the core research mission of the Brady: making new discoveries to advance the field and improve the lives of patients. The Brady is unique, as we have renowned experts representing every subspecialty area in urology. The Brady is a leader and forward-thinking institute of excellence that strives to push boundaries, expand horizons, and challenge the current dogma in our field. I look forward to showcasing the ever-growing strengths and future directions of the Brady in *Discovery*."

A major part of the Brady's success, he adds, has been made possible because of philanthropy. "It is wonderful to see so much support from the patients and friends of the Brady. That is something really special and part of Dr. Walsh's strong legacy, as well. It is my honor and privilege to carry this legacy forward by taking the helm of *Discovery*." ■

Active Surveillance for Prostate Cancer and Family History

Two men have low-grade prostate cancer, limited Gleason 3+3 disease, and both are good candidates for active surveillance (AS). But their risk may not be the same, a new Brady study has found.

Investigators led by former fellow Claire de la Calle, M.D., and Christian Pavlovich, M.D., the *Bernard L. Schwartz Distinguished Professor of Urologic Oncology*, found that men with a first-degree family history of prostate cancer face a higher risk of cancer progression during active surveillance for low-grade prostate cancer.

In the study, published in *European Urology Oncology*, the team analyzed data from 1,421 patients to assess whether a family history of prostate or other cancer influenced the likelihood of grade reclassification on biopsy – an indication that the disease may be becoming more aggressive. "We found that men with a family history of prostate cancer, or prostate cancer plus breast, ovarian, and/or pancreatic cancer, had significantly increased risks of grade reclassification to intermediate risk of prostate cancer, including to Gleason grade group 3," says Pavlovich. However, a family history of breast, ovarian, or pancreatic cancer *alone* did not significantly raise this risk."

Good news: Even though there was a higher risk of progression in men with a family history of prostate cancer, "we found no significant association with adverse pathological features, such as high pathologic Gleason score, seminal vesicle invasion, or lymph node involvement at the time of radical prostatectomy. Their long-term outcomes after surgical treatment are not worse than those without a cancer-related family history."

Based on these findings, AS is still a good option with low-grade prostate cancer, "even among those with a family history of prostate or of some other cancers," says Pavlovich. However, these patients may need closer monitoring. "Future research may further refine surveillance recommendations, based on more extended family history or genetic markers." ■

De Marzo, Lupold, and Yegnasubramanian: *The absence of miR-21 significantly slowed prostate cancer progression.*

Meet miR-21, a Small, Powerful, and Busy Molecule in Prostate Cancer

"miR-21 may help create an environment that allows tumors to evade immune detection, which could facilitate unchecked growth."

There is a tiny world inside a tumor, says molecular biologist Shawn Lupold, Ph.D., the *Catherine and Iola and J. Smith Michael Distinguished Professor of Urology*. It's like a bustling neighborhood, with buildings, roads, utilities, businesses, and residents.

The microenvironment is made up of much more than just cancer cells, he explains. "It contains blood vessels that deliver nutrients, immune cells designed to fend off disease, supportive tissue cells, and a complex network of chemical signals that allow these cells to communicate with one another. Understanding this neighborhood is crucial because it can heavily influence the behavior of the tumor itself."

In fascinating work, Lupold, along with pathologist Angelo M. De Marzo, M.D., Ph.D., and oncology research scientist Vasan Yegnasubramanian, M.D., Ph.D., have begun to uncover the significant role of a small but powerful molecule known as microRNA-21 (miR-21) within this dynamic environment. This study represents the first comprehensive analysis of any microRNA's impact on all the different cell types that make up this tiny neighborhood.

"Cancer cells are incredibly manipulative," says Lupold. "They don't operate in isolation. Instead, they actively reshuffle the components of their environment — similar to a corrupt business that gradually takes over and transforms an entire neighborhood to serve its own needs." One of the key backroom players in this process may be miR-21 – known to be elevated in various cancers, including prostate cancer.

In this study, the investigators used a specialized mouse model that closely mimics the aggressive nature of human prostate tumors. "We found that miR-21 becomes highly active in the surrounding support cells during crucial moments when prostate cancer begins to invade surrounding tissues."

By "knocking out" the miR-21 gene in this model and employing advanced techniques including single-cell RNA sequencing, the team discovered that the absence of miR-21 significantly slowed cancer progression. "Mice lacking miR-21 exhibited smaller tumors compared to their counterparts with normal miR-21 levels," says De Marzo. "This finding underscores how miR-21 helps the cancer cells thrive not only by influencing their growth, but also by altering the behavior of surrounding cells."

Restraining the immune system: One particularly striking revelation was how miR-21 influences the immune landscape within the tumors. Before the body can fight off cancer, its immune cells must recognize the presence of an enemy. "Our findings suggest that miR-21 may help create an environment that allows tumors to evade immune detection, which could facilitate unchecked growth," says Lupold.

Additionally, the team found that miR-21 influences the signaling pathways in the stroma, the supportive tissue that forms part of the tumor's neighborhood. "By adjusting these pathways, miR-21 helps create a nurturing environment for cancer growth," says Yegnasubramanian.

Understanding the intricate and multifaceted ways miR-21 and other microRNAs interact with various cell types within the tumor microenvironment "opens doors to potential new therapies that target not just the cancer cells, but also the surrounding support system," says Lupold. "This study represents a promising step toward harnessing the power of microRNAs to improve cancer care."

Other scientists who participated in this study include Kenji Zennami, Mindy Graham, Shireen Chikara, Polina Sysa-Shah, Fatima Rafiqi, Rulin Wang, Bulouere Abel, Qizhi Zeng, Timothy Krueger, Nate Brennen, Sudipto Ganguly, Jelani Zarif, Brian Simons, Ted DeWeese, and Fernanda Caramella Pereira. ■

Fibroblast Activation Protein in Prostate Cancer

Higher-grade, more advanced cancer contained more FAP, suggesting its potential role as an indicator of tumor aggressiveness.

Fibroblast Activation Protein (FAP) is an enzyme that breaks down other proteins. "In normal tissues, FAP is quiet and almost completely undetectable," says scientist Nathaniel Brennen, Ph.D. "It only really shows up when your tissues need repair, like when you get an injury and your body needs to heal."

FAP also shows up, a recent Brady study has found, in the presence of inflammation or cancer in the prostate – and it is expressed at greater levels in aggressive prostate cancer. In this study, published in *Pathology*, senior investigators Brennen, Srinivasan Yegnasubramanian, M.D., Ph.D., Angelo De Marzo, M.D., Ph.D., and team used immunohistochemistry to analyze FAP's expression in normal and malignant prostate tissues.

"We found that FAP was largely absent in normal prostate tissue, but significantly elevated in areas of proliferative inflammatory atrophy (PIA), a potential precursor to cancer," says Brennen. FAP was present in all of the prostate cancer samples they studied, "although expression levels varied widely within each tumor. Notably, higher-grade, advanced cancer contained more FAP, suggesting its potential role as an indicator of tumor aggressiveness."

The study, spearheaded by lead author, Fernanda Caramella-Pereira, M.D., also identified higher FAP levels in tissues rich in immune cells called M2 macrophages – suggesting FAP may recruit these cells as camouflage to shield the prostate cancer from attack by the immune system.

The findings support the idea put forth many years ago by team members that PIA represents regions of cellular injury and remodeling in the prostate, in response to inflammation, that can serve as a hotbed for cancer cells to develop. "We believe FAP could be a promising potential target for molecular imaging and drug therapies in prostate cancer," says Brennen.

Other investigators on the study include Qizhi Zheng, Jessica Hicks, Sujayita Roy, Tracy Jones, Martin Pomper, Lizamma Antony, and Alan Meeker. ■

A Cancer-Causing Gene Mutation and its Achilles' Heel

The HOXB13 X285K mutation, found mainly in men of West African descent, relies heavily on male hormones – which makes it more vulnerable to hormonal therapy.

Men who are born with a rare genetic change, the X285K mutation of the *HOXB13* gene, are not only more likely to develop prostate cancer, but to have an aggressive form of it. In encouraging news, Brady scientists have discovered that this mutation has an Achilles' heel: because cancers with this mutation rely heavily on male hormones (called androgens), they are more susceptible to hormonal therapy.

In a recent study, "we looked for prostate cancer patients who carry the X285K mutation and who were treated with hormone-blocking therapies," says research associate Mayuko Kanayama, M.D., Ph.D. "Although this mutation is rare – found in about one to two percent of prostate cancer cases, mainly in West African men – we were able to find 21 patients with this mutation, and had detailed treatment records for six of them."

They found that although men with this mutation tended to have high-grade prostate cancer with aggressive features similar to those in men with a faulty *BRCA2* gene, "these patients generally show favorable and longer responses to therapies targeting the androgen receptor (AR)," drugs such as enzalutamide and abiraterone, says Kanayama. "Our results suggest that men with the X285K mutation may especially benefit from treatments that target male hormones, because their cancer depends more on these hormones. Since this is the first study to investigate how patients with this mutation respond to treatment, we plan to conduct further research to confirm these findings and determine if the mutation predicts who will benefit more from hormone-blocking therapies."

Because of research conducted at the Brady, "several genetic testing labs now list the *HOXB13* X285K mutation as one that likely increases prostate cancer risk," adds Kanayama. "This is now being reported on genetic tests, and our findings could help doctors and patients choose more personalized treatments in the future." These results underscore the importance of germline genetic testing for all men with metastatic prostate cancer, "and offer new hope for a population disproportionately affected by the disease."

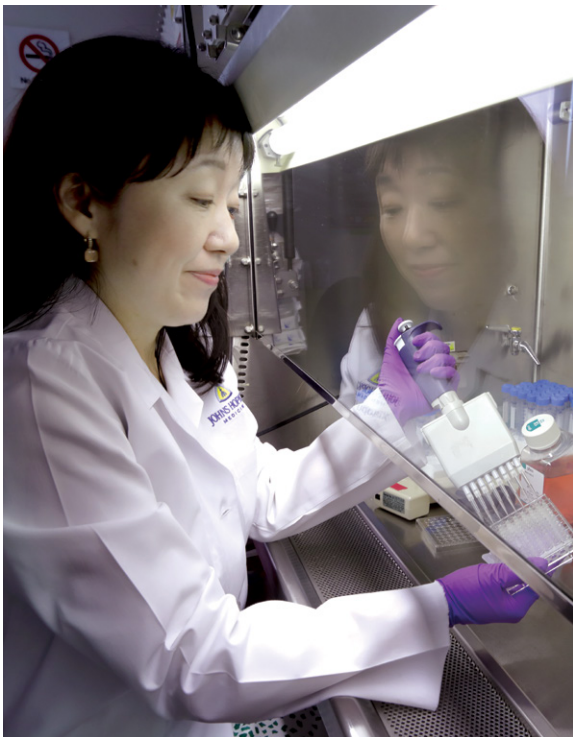
This work was reported in *Prostate Cancer and Prostatic Diseases*. Kanayama, first author of that paper, also presented this research in a poster session at the Prostate Cancer Foundation's annual scientific conference. ■

TWO MORE GENES OF INTEREST

Scientist Mayuko Kanayama, M.D., Ph.D., has received a Schaufeld Program award to conduct pilot studies of two genes: *MMS22L* and *TONSL*. "The products of these two genes act together to repair DNA," says Kanayama. "But a change in these genes may result in a defective product, and may compromise DNA repair."

These alterations can raise a man's risk of getting prostate cancer – but here again, there may be an Achilles' heel: "They also may sensitize the cancer cells to effective treatments," Kanayama says. She and colleagues have identified rare inherited mutations in both of these genes that are noteworthy for their links to specific ancestry: "For *MMS22L*, individuals of Jewish heritage may benefit from genetic testing for this mutation," which is more common in this population. "For *TONSL*, we found a novel mutation limited to men of African ancestry."

TONSL functions through *MMS22L*, Kanayama explains. The pilot study will help shed light on the interaction and activity of these genes, which one day may be helpful biomarkers to help shape treatment decisions in prostate cancer. ■



Kanayama: *Men with the X285K mutation respond better to prostate cancer therapies targeting the androgen receptor.*

MADE POSSIBLE BY GENEROUS PHILANTHROPY

More Research, Clinical Trials Coming to Sibley

In a time of uncertain federal funding for medical research, "there's a need now for philanthropy that we haven't had before."

Brady physicians at Sibley Memorial Hospital in Washington, D.C., offer world-class care. Now, thanks to generous philanthropy, Sibley urologists and urologic oncologists will also be able to conduct more research, and their patients will be able to take part in more clinical trials.

"If you are a patient with a urological disease and there is a clinical trial that you want to be part of, chances are that you can find it at Hopkins," says Urologist-in-Chief Mohammad Allaf, M.D., "Some of these are Brady science-initiated trials, answering important questions for our own home-grown investigations. Others are evaluating new drugs or new technology, testing them against the standard of care. But we have not been able to offer them all at Sibley."

Sibley, a trusted community hospital that has long served the National Capital Region, has lacked space and infrastructure for academic medical research. "We want to do more research there," says Allaf, "and because of investment by generous donors, we can now expand our footprint in clinical trials and representation from Sibley patients in our biorepository."

The main Brady biorepository is a rich treasure trove of tissue, blood, urine, hair, and cell samples, genetic material and proteins. A new biospecimen collection lab is already being built and equipped at Sibley, says urologist Armine Smith, M.D., Sibley's Director of Urologic Oncology.

The robust bladder cancer research program at Sibley includes studies of survivorship, developing biomarkers that can be seen in blood and urine, and correlating them with tumor removal surgery. In a collaborative project with the National Institutes of Health, Smith and medical oncologist, Jeannie Hoffman-Censits, M.D., are also studying changes in the microbiome in patients with bladder cancer. "Our Women's Bladder Cancer program at Sibley is unique," says Smith. "We have education, support groups, and clinical trials specifically for women," who are often overlooked when it comes to bladder cancer.

"The Sibley lab we built not only collects but processes samples, and has a limited but meaningful ability to do basic experimentation," Smith continues, "and I hope to further advance our capabilities on-site in the near future. For more advanced work we collaborate with Baltimore," but she notes that Sibley is not simply a "pass-through site." In fact, "we have our own internal review boards separate from the main Hopkins campus, and regularly serve as a site for joint studies. I am proud of the scope and independence of the work happening here."

Rana Harb, M.Sc., leads an army of about 20 people who manage the urology clinical trials unit and Brady biorepository. "At Sibley, we mostly use shared storage space with the Oncology Department," she says, "and most samples are shipped to the main campus in Baltimore. This support will allow us to have a bigger space for Urology specifically. We will be able to collect more samples for more projects that we're working on in prostate, kidney, bladder, and testicular cancer, and have them processed and stored at Sibley. Expanding the space and having extra resources will help so many projects."

Beyond collecting and storing specimens, the urology team at Sibley is working to expand its reach in the community by offering more clinical trials. Brady at the main Hopkins campus offers 35 to 40 clinical trials at any given time, compared to about five to eight at Sibley, Harb continues. "We are not able to offer all of these at Sibley due to limited space and equipment. You need space to store medications, which sometimes need to be kept in freezers that are not available at Sibley right now. Dr. Smith tried to open a study for bladder cancer, but there wasn't a freezer that could handle the study drug, and it's not stable enough to transport. We opened it at the main campus instead, making the drug inaccessible to some patients in the D.C. area." Soon, many patients at Sibley won't need to drive all the way to Baltimore to take part in cutting-edge trials. "With this support, we are very excited to expand to do full-scale scientific discovery."

The gifts that made this possible come from Judy and Peter Kovler and from Leo and Judy Zickler. Both of these couples live in the D.C. area, have strong ties to Johns Hopkins and to Sibley as patients, and have given very generously to support many projects for decades.

The Zicklers have been supporting the Brady with gifts for more than 25 years. In fact, their donation of a sophisticated piece of equipment that enables microsurgeries is named after their great-granddaughter: Kara's Microscope. "We have focused on gifts that can nudge researchers in a direction they want to go," says Leo Zickler. "We don't tell them where they should go;

Harb *(on opposite page, center) with (L-R) Sara Naizghi, Ashley Coard, and Riley Haines, part of her army of 20 people who manage the urology clinical trials unit and Brady repository.*

Smith *(left):* *"I am proud of the scope and independence of the work happening here."*

we just do something to help them get started. Then that tends to generate its own momentum."

The Kovlers have served on boards at Hopkins, Sibley, the D.C. Hospital Association and the Foundation for the National Institute of Health, and in addition to gifts to Johns Hopkins from the Judy and Peter Blum Kovler Foundation, they have established a professorship in breast cancer at Sibley and one in pancreatic cancer research at Hopkins. "The doctors at Sibley are great," says Judy Kovler; "they just need the opportunity to do more research."

"One of the great things about giving to Hopkins medicine is the ripple effect," says Peter Kovler. "You're giving to something local, and something regional, but it's an unusual opportunity to give to something that also has a national and international effect." Private philanthropy is needed now more than ever, he adds. "I've never seen a time where it's more important for people in the private sector to step up." In a time of uncertain federal funding for medical research, "there's a need now for philanthropy that we haven't had before." ■

Ashkenazi Jewish Men and Prostate Cancer

Hopkins-led research uncovers a genetic mutation with a silver lining

Imagine a zipper: it works great, as long as the metal tracks are perfectly lined up. But if just one tiny piece of metal goes askew, the whole zipper gets derailed.

Something similar can occur in DNA: it's called a "frameshift mutation," and what happens, explains molecular geneticist William Isaacs, Ph.D., is like "adding or deleting letters from words in a sentence. The words become skewed, and the meaning is corrupted." Isaacs, recently retired as the *William Thomas Gerrard, Mario Anthony Duhon, and Jennifer and John Chalsty Professor of Urology*, is the lead author of a Hopkins-led study published in *European Urology Focus*. In it, he and colleagues reported the discovery of a frameshift mutation that has important implications for men of Ashkenazi Jewish ancestry.

This mutation, called F722fs, happens in a gene called *MMS22L* – a DNA repair gene, similar to the BRCA genes, whose job is to fix errors in the genetic code. When these repair genes are out of service, those errors don't get fixed. In this case, "men with the F722fs mutation have a higher risk of developing certain types of cancer, including prostate cancer," says Isaacs. *But there's a silver lining*: drugs called PARP inhibitors (olaparib, rucaparib, and others) specifically target and are more effective in cancers with this kind of genetic damage. Cancers with a DNA repair gene mutation depend on a protein called poly (ADP-ribose) polymerase, or PARP, which acts as a sort of genetic tool kit to keep them going. PARP inhibitors block access to these patch-up repairs – so the cancer cell can't divide, and dies.

In the study, the team looked for 65 known cancer-linked inherited mutations, called "loss of function (LoF) variants," in 3,717 men who had prostate cancer and were treated with prostatectomy at Johns Hopkins, compared to a control group of 103,221 men from around the world, using information from the vast Genome Aggregation Database.

Initially, "we found three genes with LoF mutations where the men had significantly higher rates of prostate cancer than in the control group," says Isaacs. To validate this finding, they looked at those three genes in two UK databases of men who had been treated for prostate cancer and a control group. "We found that one of these genes, *MMS22L*, was linked to higher rates of prostate cancer." In further study, the team found that "all the men with prostate cancer from the Hopkins and UK groups who had a faulty *MMS22L* gene had this same F722fs variant. Importantly, an examination of ancestry-informative markers revealed that all carriers were of Ashkenazi Jewish ancestry."

They broadened their search again, looking at data from Ashkenazi Jewish men in three other patient groups – University of Michigan/Duke University, NorthShore University HealthSystem, and GoPath Labs – and again found a higher risk of prostate cancer in men with the F722fs variant. "Taken all together, we found a significantly strong correlation between being born with an F722fs mutation in the *MMS22L* gene and having a greater risk of developing prostate cancer."

"Taken all together, we found a significantly strong correlation between being born with an F722fs mutation in the MMS22L *gene and having a greater risk of developing prostate cancer."*

Like having a bad *BRCA2* gene: Men who inherit a mutated *MMS22L* gene "are not only more likely to develop certain cancers, including prostate cancer – but possibly to develop more aggressive cancer, and to develop it at a younger age," says Isaacs. "On the other hand, recent findings from other researchers at Harvard strongly suggest that the *MMS22L* gene, like a mutated *BRCA2* gene, makes a person more responsive to PARP inhibition. It may be that the F722fs mutation contributes to PARP sensitivity as well."

In future research, the team will seek to confirm these findings using independent data sets. In addition, Isaacs and the team hope to explore the potential role of the F722fs mutation as a target of genetic screening, and also as a predictor of response to PARP-inhibiting drugs.

This work was supported by the U.S. Department of Defense, the Ambrose Monell Foundation, and the Patrick C. Walsh Hereditary Prostate Cancer Fund. ■

Denmeade: *Tackling the complex ways in which prostate cancer evades treatment.*

SPORE Grant to Tackle New Approaches to Advanced Prostate Cancer

The Prostate SPORE Program aims to turn laboratory discoveries into new treatments to help men fighting advanced prostate cancer.

The Sidney Kimmel Cancer Center and Brady Urological Institute have received a prestigious five-year SPORE (Specialized Programs of Research Excellence) grant from the National Cancer Institute, totaling over $11 million.

"This is the largest program grant centered around one disease that anyone can get," says Mohammad Allaf, M.D. "Only eight of these grants are awarded across the entire country," placing Johns Hopkins among a select few institutions nationwide recognized for their innovative work in prostate cancer research.

This is not the Brady's first SPORE grant, Allaf notes. But "this recognition of our efforts in prostate cancer while we are also building our strengths in other urologic diseases, is a badge of honor for our urologists, medical oncologists, radiation oncologists, and basic scientists."

Under the leadership of medical oncologist Samuel Denmeade, M.D., the *R. Dales Hughes Professor of Oncology* and Director of the Johns Hopkins Division of Genitourinary Oncology, and scientist Shawn Lupold, M.D., the Prostate SPORE Program aims to turn laboratory discoveries into new treatments to help men fighting advanced prostate cancer. The research will tackle the complex ways in which prostate cancer cells evade treatment, focusing on factors that contribute to metastasis and treatment resistance. The SPORE projects include:

Expanding Bipolar Androgen Therapy (BAT), led by Denmeade and pathologist Angelo M. De Marzo, M.D., Ph.D. Testosterone is a major driver of prostate cancer, and standard hormonal therapy attacks cancer by shutting down male hormones."But prostate cancer can get used to this environment," says Denmeade, "and can learn to grow in the absence of male hormones. BAT shakes up the cancer. It alternates shutting down male hormones with slamming the body with high doses of testosterone, making cancer more vulnerable to treatment."

When Denmeade and medical oncologist Mark Markowski, M.D., Ph.D., explored this idea several years ago, people thought they were – well, batty. "This Hopkins-initiated, novel treatment seemed controversial at first," says Allaf. "But initial funding from the Patrick C. Walsh Prostate Cancer Research Fund, which supports high-risk, high-reward ideas, helped the team gather promising data that led to larger studies," showing that BAT can be safe and effective, leading to improvements in patients' quality of life.

In this project, researchers will combine the one-two punch of BAT with a third weapon: a drug called ZEN-3694, which targets a protein that helps cancer cells grow. They also will analyze patients' tumor samples "to help us understand which individuals respond best to the treatment," Denmeade says.

Helping the Body Fight Cancer: This project is led by medical oncologists Eugene Shenderov, M.D., Ph.D., Drew Pardoll, M.D., Ph.D., and Ken Pienta, M.D. "The goal," says Lupold, "is to boost the immune system to fight prostate cancer by targeting B7-H3," a protein produced in higher amounts by aggressive prostate cancer cells. The team will investigate two experimental treatments: a highly precise antibody drug conjugate that delivers a cancer-fighting agent directly to the tumor, and a monoclonal antibody drug enoblituzumab, which boosts the immune response against cancer.

Expanding the use of PARP Inhibitors: PARP inhibitor drugs such as olaparib can be effective in prostate cancer – but only in patients who have specific gene mutations related to DNA repair. In this project, led by oncologists Vasan Yegnasubramanian, M.D., Ph.D., and Michael Carducci, M.D., investigators will combine olaparib with decitabine, which protects DNA from certain cancer-caused changes. "We would like to expand the use of PARP inhibitors to a wider group of patients," says Denmeade. The team hopes "the combination of decitabine with olaparib will create a "triple threat" against cancer by damaging its DNA, activating the immune system against the tumor, and reducing the activity of cancer-promoting signals." The investigators will evaluate this drug combination in a clinical setting through the ongoing PARENT (PARP Inhibitor plus Epigenetic Therapy) trial. ■

Beyond Hormones: Innovative Strategies to Combat Prostate Cancer

CRM1 is an important linchpin that keeps the wheel of advanced prostate cancer turning. A drug called Selinexor, already approved for treating other cancers, targets it.

Hormonal therapy in prostate cancer is like a dynamic game of chess. Male hormones, called androgens, drive and sustain the cancer. Androgen deprivation therapy – shutting off testosterone with drugs such as leuprolide or goserelin – can slow or even stop this growth.

However, prostate cancer is resourceful: it can latch onto proteins called androgen receptors (AR), and use them to make the fuel it needs to grow. AR signal-blocking drugs such as enzalutamide and abiraterone shut down this path.

But once again, cancer can rally, by creating a slightly different AR (called an AR-splice variant) that doesn't respond to these drugs. (Several variants, including one called AR-V7, have been identified at the Brady by Jun Luo, Ph.D., the *Alan W. Partin, M.D., Ph.D., Professor of Urology*.)

"When cancer becomes resistant to these therapies, it evolves into a more aggressive form, known as castration-resistant prostate cancer (CRPC)," says scientist Sushant Kachhap, Ph.D. "There is a need for new approaches that can target these variants and other mechanisms that encourage the AR in CRPC, to make treatment more effective."

In exciting research, Kachhap and colleagues may have found one. A new study from his lab, published in *Federation of American Societies of Experimental Biology (FASEB)*, focuses on a protein called CRM1, "which plays a role in stabilizing the AR at both the RNA and protein levels," Kachhap explains. "This is especially important, because AR-splice variants originate at the RNA level."

CRM1, it turns out, is an important linchpin that keeps the wheel of advanced prostate cancer turning. By using a drug called Selinexor, which targets CRM1 and is *already approved for treating other cancers*, Kachhap's team was able to destabilize both the AR protein and AR variants in prostate cancer cells. "Selinexor works by preventing the transport of proteins that keep the AR, ultimately inhibiting its function."

"What's even more promising," Kachhap continues, "is that CRM1 also influences other cancer-associated proteins and pathways, including DNA repair. Targeting CRM1 offers new opportunities for innovative drug combinations beyond traditional hormonal therapy. Although further research is needed to test this approach in pre-clinical models, the early signs are very encouraging." This work was supported by the Patrick C. Walsh Prostate Cancer Research Fund and by the Department of Defense. " ■

Could a New Bladder Cancer Drug Work on Prostate Cancer, Too?

Nectin-4 is commonly present in prostate tissue – but a lot more of it is expressed in cancer than in normal cells.

One of the most promising new treatments for bladder cancer involves a protein called Nectin-4. Expressed in high amounts in bladder cancer, Nectin-4 is the target of an antibody drug conjugate called enfortumab vedotin (EV). In exciting research, a Brady team asked a new question: Could Nectin-4 also be a treatable target in aggressive prostate cancer?

"Many men with bladder cancer also develop prostate cancer," says genitourinary cancer specialist Jeannie Hoffman-Censits, M.D. To find out whether this same protein could be involved in both types of cancer, Hoffman-Censits, pathologist Ezra Baraban, M.D., and colleagues recently conducted an extensive study involving samples from 302 prostate cancer patients. Using a technique called immunohistochemistry, the researchers measured the levels of Nectin-4 in both normal and cancerous prostate tissues.

They found that Nectin-4 is commonly present in prostate tissue – but a lot more of it is expressed in cancer cells than in normal cells. The vast majority – about 91 percent – of the prostate cancer cases the team studied showed some Nectin-4 expression, "with cancer cells typically showing intense protein levels across various grades of prostate cancer," says Baraban. "Remarkably, ductal adenocarcinoma, a rare and aggressive form of prostate cancer, exhibited especially high levels of this protein."

These findings, published in *The Prostate*, point to the potential use of Nectin-4-targeting EV as a treatment for prostate cancer. More studies are needed, the researchers caution, but the concept is promising. Also, notes Baraban, "this study highlights the importance of investigating existing therapies for potential use across different cancer types." ■

Kenneth Pienta, M.D., whose distinguished career has focused on understanding how cancer metastasizes, is the Brady's new Director of Innovation and Strategy, and Co-Director of the Prostate Cancer Research Program at the Sidney Kimmel Comprehensive Cancer Center. He is also Co-Director, with Sarah Amend, Ph.D., of the Johns Hopkins Cancer Ecology Center. "By understanding how cancer acts as an invasive species in the patient," he says, "we can develop innovative strategies to detect, prevent, and treat tumors." *Portrait by Lisa Egeli.*

Treatment Resistance in Prostate Cancer

This study, while documenting ways that prostate cancer becomes resistant to treatment, shows the dedication and resourcefulness of this patient's Hopkins oncology team, who never gave up.

Prostate cancer is heterogeneous: it is a hodgepodge of different kinds of cells, some worse than others. This often means the cancer becomes resistant to therapy – but sometimes, this change opens up a new avenue of treatment that wasn't there before.

In a recent study, published in *NPJ Precision Oncology*, through genetic analysis Brady investigators closely followed the evolution of one man's metastatic prostate cancer over more than seven years of treatment, looking for mechanisms by which his cancer became resistant to various therapies. The man was diagnosed at age 76 with a very high PSA (5,786 ng/ml) and widely metastatic, high-grade (Gleason 9) cancer.

"We determined that the patient's original primary tumor contained two separate types of prostate cancer," says medical oncologist Laura Sena, M.D., Ph.D., the study's senior investigator. "Although the dominant type of prostate cancer was effectively treated by the first approaches, unfortunately, the patient was not cured because the less dominant type of prostate cancer persisted, grew, and eventually spread widely."

The initial dominant type of prostate cancer was a rare subtype with mismatch repair deficiency. Because of this, the patient was treated on a clinical trial with an immune checkpoint-inhibiting drug, nivolumab. At first, he responded well, with his PSA dropping down to only 1 ng/ml, and scans showing a marked decrease in tumor volume. But over the next four months, his PSA began to rise. "Enzalutamide was then added to nivolumab treatment, which resulted in a sustained response over several years. Then, unfortunately, the cancer began to progress."

This study, while documenting the patient's cancer, shows the dedication and resourcefulness of his Hopkins oncology team, who never gave up. It also highlights the variety of drugs now available to men with metastatic prostate cancer. Next, the patient was treated with more chemotherapy, bipolar androgen therapy, a second trial of enzalutamide, and nivolumab in combination with ipilimumab, "without notable response to any agent."

At this point, genetic analysis of a biopsy of an enlarged cervical lymph node revealed a surprise: a mutation in his *BRCA2* gene. Sena's team then sought the help of scientist Rachel Karchin, Ph.D., and her team, who are experts in genetic analyses of tumor evolution. Using PictographPlus software, developed in the Karchin Lab by postdoctoral fellow Jiaying Lai, Ph.D., the genetics of this lymph node were compared with the original tumor samples. "Dr. Lai demonstrated that this mutation was present in a small portion of the primary tumor at diagnosis," says Sena. Like tiny bad apples that go on to spoil the whole bushel, over seven years the cancer cells with this mutation expanded to become the dominant cancer type.

"Fortunately, recognizing this evolution of his cancer enabled him to receive treatment with a targeted medication that inhibits a molecule called PARP, which was highly effective," says Sena. "This case provides evidence that therapy resistance can occur due to a process called selection, whereby a small population of resistant cancer cells are present before therapy begins. Cancer progresses despite treatment as these resistant cells grow and spread." Sena's laboratory is now focusing on "new strategies to prevent therapy resistance, in light of this new knowledge."■

Sena and Karchin: *Comprehensive study of a man's difficult-to-treat prostate cancer found a new way to help him.*

2025 AWARDEES

Sarah Amend, Ph.D.
The Keith L. Bremer Scholar,
Department of Urology

Angelo De Marzo, M.D., Ph.D.
The Donald E. Graham Scholar,
Department of Pathology

Sushant Kachhap, Ph.D.
The Beth W. and A. Ross Myers Scholar,
Department of Oncology

Rajendra Kumar, Ph.D.
The Virginia and Warren Schwerin Scholar,
Departments of Biochemistry and Molecular Biology

Shawn Lupold, Ph.D.
The William and Carolyn Stutt Scholar,
Department of Urology

Christian Pavlovich, M.D.
The R. Christian B. Evensen Scholar,
Department of Urology

Arun Rai, M.D., M.B.A., M.S.
The Mr. and Mrs. Robert Baker Family Foundation Scholar
Department of Urology

Eugene Shenderov, M.D., Ph.D.
The George and Mary Nell Berry Scholar,
Department of Oncology

Swaroop Vedula, M.B.B.S., M.P.H., Ph.D.
The Charlton C. and F. Patrick Hughes Scholar,
Malone Center for Engineering in Healthcare; The Johns Hopkins Data Science and AI Institute

Read About the Research You Have Helped Make Possible.

How important is seed money? Priceless!
Many of the scientists featured in Discovery jump-started their research careers with awards from the Patrick C. Walsh Prostate Cancer Research Fund. In fact, some of the major advances in prostate cancer research have been made possible by these investments.

This Fund owes its existence entirely to grateful 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.

WITHOUT YOU, THEIR WORK WOULDN'T BE POSSIBLE.

SARAH AMEND, PH.D.

When Metastatic Cancer Cells Play Hopscotch

"We found that cells that survive after therapy bypass mitosis – growing and replicating DNA without dividing into two daughter cells."

Why does metastatic prostate cancer become resistant to treatment? As it evolves, it becomes more efficient, and its growth is streamlined. In fact, it plays its own version of hopscotch – skipping right over a critical step in its growth cycle.

"Most cancer cells progress through a proliferative cell cycle," says scientist Sarah Amend, Ph.D.: "growing, replicating DNA, and undergoing mitosis and cell division." But cancer cells that become treatment-resistant change their habits: "We found that cells that survive after therapy bypass mitosis – growing and replicating DNA without dividing into two daughter cells."

Why does this hopscotch, or "mitotic skipping," happen? Amend and colleagues have found an important clue. "Centrosomes are the microtubule-organizing centers of the cell; most cells have one to two centrosomes," she explains. "We observed that cells that survive therapy have more centrosomes, and they are clustered together.

There is evidence that centrosomes can act as physical platforms for signaling molecules," and that these bunched-up centrosomes facilitate rapid-fire cell signaling, "including for cell cycle regulators. We hypothesize that the amplified and clustered centrosomes in therapy-resistant cancer cells enable cell survival by acting as signaling platforms for key regulators of the mitotic skip."

With this grant, Amend and colleagues propose to study the proteins expressed in the centrosomes of therapy-resistant cancer cells and map the key signaling molecules necessary for mitotic skip. Then, they plan to therapeutically disrupt centrosome clustering, "to drive cells into mitosis and kill the otherwise resistant cancer cells." ■

ANGELO DE MARZO, M.D., PH.D.

Chronic Inflammation and Prostate Cancer

"We recently found that inducing inflammation in older mice appears to accelerate the development of prostate cancer," but this is not the case in younger mice.

Inflammation is often a good thing. It's how the body protects itself against infectious agents and fixes tissue damage after an injury. "Normal inflammatory responses are self-limiting and resolve once the infection is cleared or the damage is repaired," says pathologist Angelo De Marzo, M.D., Ph.D. But long-term inflammation is not so good.

"Chronic inflammation persists beyond when it is useful, and is a feature of many diseases," De Marzo continues. "Paradoxically, immune cells can sometimes damage normal cells, leading to a vicious cycle of injury and repair." Chronic inflammation is a known factor linked to specific types of cancer. For example, patients who have the inflammatory condition, ulcerative colitis, are at higher risk for developing colon cancer. "There is evidence that more than 25 percent of all cancers result from chronic inflammation."

Chronic inflammation is "exceedingly common" in the prostate, De Marzo adds, "and has long been suspected of playing a role in the development of prostate cancer – however a true causal role has not been established." De Marzo and co-investigators Charles Bieberich, Ph.D., and Srinivasan Yegnasubramanian, M.D., Ph.D., hope to find this link.

"We genetically engineered a mouse model in which prostate inflammation can be induced," says De Marzo. "We recently found that inducing inflammation in older mice appears to accelerate the development of prostate cancer," but this is not the case in younger mice. With this grant, the team plans to explore this age gap further, and to understand more about how prostate cancer develops. Their results, De Marzo hopes, "will provide a solid foundation to justify future experiments aimed at reducing chronic prostate inflammation in men. We also believe this work could lead to public health recommendations to lower prostate cancer risk." ■

SUSHANT KACHHAP, PH.D.

Why Do Some Tumors Respond Dramatically to BAT?

Some men respond better than others to bipolar androgen therapy (BAT). This paradoxical approach, developed at Hopkins, alternates androgen deprivation therapy (ADT) – suppression of testosterone and other androgens, or male hormones – with the exact opposite approach, a course of high-dose testosterone.

Why doesn't BAT work equally well on every man with metastatic castrate-resistant prostate cancer (mCRPC)? The Hopkins scientists who pioneered this approach believe they have found an answer to this riddle. "To date, our group has treated 330 patients across four phase II studies using BAT, documenting safety as well as significant clinical activity in a subset of men with mCRPC," says scientist Sushant Kachhap, Ph.D. In preliminary studies with co-investigators Samuel Denmeade, M.D., Nathaniel Brennen, Ph.D., and Eugene Shenderov, M.D., Ph.D., "we have found that proteins called epi-transcriptome modulators in prostate tumors dictate immune cell response to BAT."

With this grant, the team hopes to understand how these proteins function in response to BAT, and to shed light on why certain tumors respond dramatically to BAT. "We believe this work will uncover novel protein markers that can help predict which patients will respond to BAT," says Kachhap. The investigators also plan to study the combination of BAT with immunotherapy. "This is the first study to prospectively assess epitranscriptomic modulators as biomarkers of response to BAT in prostate cancer," says Kachhap. "Most importantly, we aim to study a never-before tested idea with a potential transformative impact on the field. We hope our findings will help us offer BAT in an informed manner, and help us devise strategies to provide benefit of this approach to a wider group of men with mCRPC." ■

RAJENDRA KUMAR, PH.D.

Clumping Androgen Receptors and BAT

There are two ways to stop androgen (male hormone) activity in prostate cancer: one is androgen deprivation therapy (ADT), which shuts down testosterone and other hormones. The other is to block a protein in cancer cells known as the androgen receptor (AR), which is activated by androgens. This combined approach can be effective, sometimes for many years. However, over time, most patients develop resistance, leading to metastatic castration-resistant prostate cancer (mCRPC).

In bipolar androgen therapy (BAT), "instead of blocking androgens, we cycle between very high and very low testosterone levels to disrupt cancer cell growth," explains scientist Rajendra Kumar, Ph.D. "Early clinical studies have shown encouraging results, but not all patients respond to BAT (see previous story), and its effects vary in duration and strength."

With co-investigator Samuel Denmeade, M.D., Kumar will explore a new idea that could expand BAT's impact. "We hypothesize that when prostate cancer cells are exposed to high levels of androgens (also known as supraphysiological androgens, or SPA), the AR proteins become overly stabilized and start to clump together, or aggregate, inside the cells."

A similar process happens in a rare genetic condition called Kennedy's disease, where abnormal AR aggregation causes damage to cells, he says. "We believe that in prostate cancer, these AR aggregates trigger a type of cellular stress known as endoplasmic reticulum (ER) stress, which can ultimately lead to cancer cell death." However, Kumar notes, some cancer cells may resist this stress by activating protective mechanisms. "To overcome this, we propose combining SPA with drugs that increase ER stress, thereby overwhelming the cancer cells' defenses and causing them to die – even in cases that are resistant to SPA alone."

With this grant, Kumar and Denmeade will test this strategy using prostate cancer cell lines and patient-derived organoids – miniature, lab-grown tumor models. "These models closely mimic how real tumors behave in the body, and will help us evaluate the potential of this combination therapy to improve outcomes for patients with advanced, treatment-resistant prostate cancer." ■

SHAWN LUPOLD, PH.D.

A Molecular Mashup in Advanced Prostate Cancer

"If we are successful, our findings could transform CRPC into a manageable disease."

In Greek mythology, the dreaded Chimera was a terrible mashup: a hybrid lion with a goat's head sticking out of its back, and a snake's head on its tail. In recent research, Brady scientists have found that treatment-resistant prostate cancer (metastatic castration-resistant prostate cancer, or mCRPC) has a chimera, too.

"We have discovered a molecular anomaly that may explain why some prostate cancer becomes untreatable," says scientist Shawn Lupold, Ph.D. With co-investigator Jun Luo, Ph.D., "we found that in mCRPC cells, genetic instructions become scrambled in an unprecedented way. Two adjacent and distinct types of genes that normally produce separate RNA transcripts, instead produce novel chimeric transcripts."

Here's what happens: A microRNA called miR-196a, which normally regulates other genes, and next-door HOX genes, which normally control tissue development, "become activated and fuse together, creating never-before-seen chimeric RNA molecules that may help cancer cells resist treatment," says Lupold. But there's good news, he adds: "These features make these chimera transcripts both a potential biomarker and therapeutic target."

With this grant, Lupold and Luo will first determine how these chimeric RNA molecules affect prostate cancer growth and resistance to treatment. Next, "we will develop diagnostic assays to detect these chimeric transcripts in patients' blood and tissue samples. Then we will engineer precision medicines called antisense oligo-nucleotides that prevent these chimeric transcripts from forming," says Lupold. "By disrupting this resistance mechanism, we may restore sensitivity to standard treatments."

This work represents a new way to understanding treatment resistance – "through aberrant RNA transcription and splicing, rather than genetic mutations," says Lupold. "If we are successful, our findings could transform CRPC into a manageable disease." ■

CHRISTIAN PAVLOVICH, M.D.

Could Testosterone Levels Predict Risk of Prostate Cancer Progression?

Some men with low-grade prostate cancer can safely remain in active surveillance (AS) for many years. Others, however, do need treatment because their cancer progresses. Could testosterone levels be a telling feature of cancer that may need treatment? Urologist Christian Pavlovich, M.D., aims to find out, with co-investigators Amin Herati, M.D., Soum Lokeshwar, M.D., M.B.A., Lori Sokoll, Ph.D., and Yuezhou Jing.

"Testosterone at baseline – when a man enters the AS program – has not yet been fully studied as a risk factor for cancer progression," says Pavlovich. With this grant, "we will examine archived blood from AS patients to see if testosterone/free testosterone levels predict their cancer getting worse. If we do find a connection, we will attempt to incorporate that into our statistical model to help counsel patients on their risk of progression on AS." ■

ARUN RAI, M.D., M.B.A., M.S.

Hello, Brady Bot: My PSA Just Went Up. What Should I Do?

"These tools could help doctors and patients make more informed decisions."

Patrick Walsh has kept careful records of every single prostatectomy patient. Building on his painstaking follow-up, for more than 40 years, the Brady has carefully tracked the outcomes of nearly 30,000 patients.

"This rich database includes detailed information such as surgical findings, PSA tests, and whether patients needed further treatment like radiation," says Clinical Director for the Division of Quantitative Science Arun Rai, M.D., M.B.A., M.S. However, that database is a product of its time, he adds. "It was built using what is now considered outdated software (Microsoft Access) and requires time-consuming manual updates, including pulling information from electronic medical records and calling patients directly. This limits how effectively researchers can use the data to improve care, and hampers our ability to leverage newer methods of data analysis."

With this grant, Rai, with co-investigators Swaroop Vedula, M.B.B.S., M.P.H., Ph.D., and Greg Hager, Ph.D., M.S., will move that database into a secure, user-friendly system called REDCap, which will allow patient information to be updated automatically from the electronic medical record. It will also let patients securely log in to report their clinical course. "This will make the data more accurate, complete, and easier to use for research," says Rai.

The long-term goal is to use this modernized database to help develop artificial intelligence (AI) tools that can learn from thousands of past patient experiences to predict how prostate cancer may behave in the future. "These tools could help doctors and patients make more informed decisions about treatment and follow-up care." ■

EUGENE SHENDEROV, M.D., PH.D.

Developing a Highly Targeted Drug for Prostate Cancer

"The drug only gets turned on inside the tumor, not elsewhere in the body."

"We are developing an antibody-drug conjugate for metastatic prostate cancer," says medical oncologist Eugene Shenderov, M.D., Ph.D. This innovative medicine combines the immune system's very own guided missile – an antibody, which can be engineered to target only very specific cells — with a powerful cancer-killing drug.

"Our project focuses on two proteins, B7-H3 and PSCA, that are found on the surface of prostate cancer cells but not usually on healthy cells – except for in the prostate, a non-essential organ," Shenderov continues. With co-investigators Sangeeta Ray, M.S., Ph.D., Nathaniel Brennan. Ph.D., and Samuel Denmeade, M.D., "we are designing our medicine to activate and kill cancer cells only when both proteins are present, like a smart key that opens only when the two locks match."

This double-targeted approach will help avoid harming healthy bystander cells, and make the drug safer and more effective. But to make the drug even safer, "we also incorporated a 'safety switch' using PSA, a protein that activates the drug," Shenderov continues. "This switch ensures that the drug only gets turned on inside the tumor, not elsewhere in the body."

With this grant, the team is testing this new treatment in the lab using prostate cancer cells and specialized mice that have human prostate cancer. "If successful, our findings could lead to better treatments with fewer side effects, potentially helping more men live longer with prostate cancer or even eliminate it entirely." ■

SWAROOP VEDULA, M.B.B.S., M.P.H., PH.D.

AI Coaching for Better Surgical Procedures

Using AI to help surgeons and surgeons-in-training improve, step by meticulous step.

Sports coaches do it routinely: they spend hours watching each game play by play, looking for ways the team can improve. "Measuring surgeons' skill and optimizing it can assure all patients with the best outcomes after surgery," says scientist Swaroop Vedula, M.B.B.S., M.P.H., Ph.D. With this grant, Vedula and co-investigators Arun Rai, M.D., M.B.A., M.S, Greg Hager, Ph.D., M.S., and Ahmed Ghazi, M.D., M.S., plan to apply artificial intelligence (AI) to videos from the Brady surgery simulation lab to help surgeons and surgeons-in-training improve their game, step by meticulous step.

"Our long-term goal is to enable objective surgical performance assessments and outcome prediction that is personalized to both patients and surgeons," Vedula says. The multidisciplinary team, building on prior work, "will develop AI models to segment surgeons' gestures and assess their skill in performing nerve-sparing dissection in robot-assisted radical prostatectomy (RARP), using 3-D printed models. Our work will provide preliminary data for an R01 on a collaborative multi-site study." ■

MORE BRADY UROLOGY CANCER NEWS

DISCOVERY IN BLADDER CANCER

GBCI 2.0: Hahn and Kates Lead New Era for the Greenberg Bladder Cancer Institute

The GBCI studies and treats all forms of bladder and upper urinary tract cancers, from the most common to the rarest forms.

Hahn and Kates: *The GBCI has always approached bladder cancer as a complex disease that spans specialties.*

In May 2014, the generosity of philanthropists Erwin Greenberg and his wife, Stephanie Cooper Greenberg, made possible the creation of the Johns Hopkins Greenberg Bladder Cancer Institute (GBCI). Nearly 12 years ago, bladder cancer was an understudied and underfunded area of urology and oncology. The Greenbergs helped meet a great need: the multidisciplinary GBCI became the first institute of its kind dedicated to improving the lives of patients with cancers of the bladder and upper urinary tract.

Under the leadership of its first director, David McConkey, Ph.D., the GBCI has done great things. Its world-class research, patient care and education, and training of young doctors and scientists have helped transform the field of bladder cancer. In 2025, McConkey became Vice Chair for Research in Urology at the University of Rochester, and Johns Hopkins has named two of its finest physician-scientists to lead the GBCI's next era: Medical oncologist Noah Hahn, M.D., and urologist Max Kates, M.D. the *R. Christian B. Evensen Professor of Urology*.

Two directors, two specialties. Because the GBCI has always approached bladder cancer as a complex disease that spans specialties, "there is very little that we do that doesn't have a multidisciplinary angle," says Hahn, "even for the earliest stages of bladder cancer," which used to be treated primarily by urologists. Metastatic bladder cancer, in turn, was long considered the sole province of medical oncologists. Not anymore.

Today, patients with metastatic cancers of the bladder and upper urinary tract *that once were considered inoperable*, after combination treatment with the antibody drug conjugate enfortumab vedotin (EV) and the immunotherapy drug pembrolizumab, are achieving "response rates higher than we've ever seen before," says Hahn. "Roughly 30 percent of patients have a complete response! Previously, that number was around five to 10 percent."

"NIGHT AND DAY"

Kates, Hahn, and colleagues are routinely navigating possibilities that did not exist a decade ago. "Unfortunately," says Hahn, "it used to be that for many patients with metastatic disease, we started them on the best chemotherapy medicines that we had, and we didn't have anything after that. I saw a lot of my patients pass away; there were only a few long-term survivors, we weren't able to predict who they were, and we didn't understand how to move that bar."

What a difference in "GBCI 2.0," as Kates calls it: Some patients who would have been considered incurable a decade ago are now doing so well that "surgery is back on the table." In patients who still have some disease in the bladder or upper urinary tract, "do we consider surgery to remove the bladder? Do we need to think about bringing in radiation? Is a cure possible?"

Better surgery. With improved surgical techniques, adds Kates, "we're very interested in finding new ways to preserve a patient's bladder, kidneys, and surrounding organs. "We are actively engaged in novel trial designs with our amazing scientists and clinicians. We believe we have the best team in the world; we're uniquely positioned to do this." And yet, he is quick to add, "While we're working to make surgery better, we're also trying to obviate the need for surgery in the first place." Kates, Hahn, and medical oncologist Jeannie Hoffman-Censits, M.D., are national leaders in clinical trials for drug development. Their goal: "How do we apply these drugs in a new way," says Kates, "to get long-term, complete responses for our patients with invasive cancers of the bladder or upper urinary tract, so surgery is not necessary?"

Several years ago, the National Cancer Institute led a landmark effort, The Cancer Genome Atlas (TCGA) project, to profile the genetic changes in cancers. "That gave us our first roadmap of the unique biologic drivers of bladder cancer," says Hahn. Next, "some of the larger pharmaceutical companies, seeing the genetic profile of

Continued from previous page >

bladder cancer coming out of the TCGA project, predicted that bladder cancer would respond well to immunotherapy. They started launching some of the first clinical trials in decades," aimed at developing drugs *specific to bladder cancer* – "not trying to get something approved in other diseases and saying, 'Let's try it in bladder cancer.' Bladder cancer was the number one priority of these trials, and thankfully, they were successful."

Much remains to be done, Hahn adds. "We haven't fixed everything. There are still unanswered questions. But where we are is night and day compared to the beginning of my career. When I was a fellow attending urologic cancer conferences and presenting an abstract," says Hahn, "you could fit everybody in the world who was doing bladder cancer research in a relatively small conference room. That has changed dramatically. Now we have conferences that are devoted only to bladder cancer. Those did not exist before. And because of that, our residents, junior faculty, and fellows are seeing opportunities and spaces for them to grow and expand their research. We no longer can fit in that small room, and that's a very good thing."

A CLINICAL TRIAL AVAILABLE FOR EVERY PATIENT

If you have bladder cancer and want to be part of a clinical trial, chances are excellent that you can find it at the GBCI. Says Kates, "We are determined to have a clinical trial available for every patient with bladder cancer, regardless of what stage they're in or what treatment they've had. We want to offer standard of care options and a cutting-edge option that they may not otherwise have access to, which may be very promising. We generally have 10 to 15 trials for bladder and upper urinary tract cancer patients. We lead these trials; we don't just sign onto them. And we help write the trials."

The GBCI studies and treats all forms of bladder and upper urinary tract cancers, from the most common to the rarest forms. Of note, "Jeannie Hoffman-Censits and Nirmish Singla have carved out a strong international presence in upper urinary tract urothelial cancers," another area that was long understudied, Hahn adds. "We're very proud of what the GBCI has accomplished in its first decade. People can be successful in their own individual silos, but not as impactful. The GBCI provides the glue to bring people together. That has created a critical level of expertise that doesn't exist in a lot of places. We also thank Erwin Greenberg and Stephanie Cooper Greenberg. They could have established this anywhere, but they chose Hopkins. We're just as excited about what the next decade holds. Things are changing fast." ■

Pathology Detective Work Reveals Lookalike Bladder Tumor

"The findings suggest... a deceptive and highly aggressive variant of bladder cancer."

Using advanced genetic testing and old-fashioned detective work, Brady pathologist Ezra Baraban, M.D., and colleagues have solved a mystery that involves an unusual, rare – and sneaky – form of bladder cancer.

Baraban had noticed a weird phenomenon in some urinary tract tumors that were sent to him for analysis: Some patients appeared to have what looked like "yolk sac tumors," a rare type of cancer that typically begins in germ cells (cells that make sperm or eggs), and is usually seen in the testes or ovaries of young patients.

But these weren't young patients; the average age was 78. "This raised a key question," says Baraban: Why were older patients getting tumors known for striking young people? "Were these truly reproductive system tumors, or could they actually be an unusual form of bladder cancer?"

To investigate, he and colleagues studied a series of these tumors that showed yolk sac-like features. "Interestingly, many of these patients had a history of bladder cancer or pelvic radiation, and the tumors appeared to arise from the lining of the urinary tract — suggesting these were a deceptive form of bladder cancer."

Baraban and colleagues then proved that in this case, looks can be deceiving: "Using advanced genetic testing, we found none of the typical markers of yolk sac tumors," he continues. "Instead, the tumors carried genetic mutations that strongly resembled those seen in aggressive bladder cancers," including changes in the *TERT* and *TP53* genes and deletions in other important regions of DNA commonly observed in bladder cancer.

"Clinically, these tumors were highly aggressive, with most patients experiencing recurrence or spread of the disease. The findings suggest that these rare tumors aren't germ cell tumors after all, but rather a deceptive and highly aggressive variant of bladder cancer." Recognizing this distinction, says Baraban, is critical for proper diagnosis and treatment, "opening the door to more effective care for patients facing these rare cancers."

This work was published in *Modern Pathology*. ■

Improving Outcomes in Advanced Bladder Cancer

"Our findings showed a significant benefit in progression-free survival with the addition of Sacituzumab chemotherapy to Avelumab maintenance."

"For patients with advanced and metastatic bladder cancer, the standard of care is platinum-based chemotherapy followed by maintenance therapy with the checkpoint inhibitor, Avelumab – particularly outside the U.S.," says medical oncologist Jeannie Hoffman-Censits, M.D.

Would it be helpful to add another chemotherapy drug to the maintenance therapy? Hoffman-Censits recently led the International JAVELIN Bladder Medley study, which looked to answer this question. This phase II clinical trial tested Avelumab alone (monotherapy) compared to Avelumab plus Sacituzumab govitecan (SG), a targeted drug conjugate. The answer, the investigators found, is yes. At data cutoff, about 51 percent of patients in the avelumab plus SG group, and 27 percent of patients in the Avelumab monotherapy group were still receiving study treatment. Progression-free survival was over 11 months in the Avelumab plus SG group, versus less than four months in the monotherapy group.

"Our findings showed a significant benefit in progression-free survival with the addition of Sacituzumab chemotherapy to Avelumab maintenance," says Hoffman-Censits. She presented the interim analysis of this study at the annual American Society of Clinical Oncology (ASCO) meeting in the spring of 2025 and was lead author of the corresponding publication in *Annals of Oncology*. ■

Easing Recovery After Bladder Tumor Surgery

"The results were clear. Patients in the ERAS group felt significantly better, reporting higher quality of recovery, less pain, fewer urinary issues, and less incontinence the day after surgery."

Transurethral resection of bladder tumor (TURBT) is a minimally invasive procedure that has a lot going for it. It's similar to colonoscopy, in that a long, thin tube is inserted through a natural opening – in this case, the urethra – and if a tumor is found, it can be diagnosed and removed during the same procedure. TURBT is minimally invasive, typically done in an outpatient setting, often described as "routine, incision-free, and well-tolerated."

ROOM FOR IMPROVEMENT

But urologist Max Kates, M.D., the *R. Christian B. Evensen Professor*, Director of Urologic Oncology at the Brady, and Co-Director of the Greenberg Bladder Cancer Institute, heard otherwise from his patients – many of whom reported that they experienced significant distress and discomfort after the procedure.

In 2023, Kates and his urologic oncology fellow Michael Rezaee, M.D., M.P.H., led a study involving 159 patients at multiple centers to characterize the side effects from TURBT and recovery from the procedure. "That study revealed that up to a third of patients suffer notable symptoms like painful or uncomfortable urination, penile or vaginal pain, suprapubic pain, and urinary urgency and frequency," plus constipation and lack of sleep. Ten percent of patients needed an urgent visit to the clinic or Emergency Department, and about 7 percent had to be admitted to the hospital. Female patients, diabetic patients, and those with more advanced tumors were especially at risk for a harder recovery.

Determined to make TURBT better, Kates and Rezaee – along with guidance from patients and their clinicians – designed a new "Enhanced Recovery After Surgery" (ERAS) protocol, which targets factors of delayed recovery – the pain, the urinary urgency and frequency, and the slow return of normal bowel and urinary function.

The new protocol was tested recently in a clinical trial called EMBRACE; 100 patients were randomly assigned either to receive standard care or the ERAS approach. Patients in the ERAS group received improved education, tailored pain management, and structured follow-up. "The results were clear," says Kates. "Patients in the ERAS group felt significantly better, reporting higher quality of recovery, less pain, fewer urinary issues, and less incontinence the day after surgery."

"With the ERAS protocol, we can provide more empathy, structure, and support to care for our patients with bladder cancer."

In addition to Kates and Rezaee, investigators on this study include Katherine Mahon, M.D., Bruce Trock, Ph.D., The-Hung Edward Nguyen, M.D., Armine Smith, M.D., Noah Hahn, M.D., and Sunil Patel, M.D., M.A. ■

New Hope for Bladder Cancer Detection: A Simple Urine Test?

"When both tests were used together, detection improved to 78 percent."

"Bladder cancer, especially in its high-grade form, is a serious and often aggressive disease. Detecting it early is key," says fourth-year Brady resident Michelle Higgins, M.D. "Unfortunately, there is no routine screening or monitoring test for bladder cancer." But thanks to Brady investigators, a new, simple urine test may be one step closer.

Higgins was part of a recent Brady study that focused on UCA1, an RNA molecule that is known to be elevated in bladder cancer. In this study, published in *Urology*, the team investigated whether the presence of this biomarker in urine could accurately identify high-grade bladder cancer.

"We tested urine from 50 patients using a lab method called RNA *in situ* hybridization (RISH) to detect UCA1 in urine samples," says Higgins. "We found that RISH detected high-grade bladder cancer in 67 percent of cases — much better than cytology (looking at bladder cells in urine) alone, which detected just 34 percent. When both tests were used together, detection improved to 78 percent."

Further research is needed to confirm these findings, but "UCA1 is showing promise as a new way to identify dangerous bladder cancers in a noninvasive way," says urologist Max Kates, M.D., senior author of the study. "It could also help monitor patients over time, and help us detect shifts from low to high-grade disease sooner." ■

New Insights on a Rare Subtype of Urothelial Carcinoma

Found: two potential targets for treating an aggressive form of bladder cancer.

"Sarcomatoid urothelial carcinoma (SUC) is an aggressive form of bladder cancer that is difficult to treat," says medical oncologist Burles ("Rusty") Johnson III, M.D. Adding to the challenge, "subtypes of bladder cancer such as SUC are excluded from clinical trials, so we don't have the data on how best to treat patients with this disease."

But there is encouraging news: In 2024, Johnson and medical oncologist Noah Hahn, M.D., reported in *Bladder Cancer* that patients with muscle-invasive SUC who receive chemotherapy before surgery have a pathologic complete response rate – no tumor present at time of surgery – of 38 percent.

After their study showed that SUC is responsive to chemotherapy, Brady investigators did further work toward understanding SUC better and improving

treatment. Johnson, with genitourinary pathologist Andres Matoso, M.D., identified differences between SUC and conventional urothelial carcinoma within eight patients who had both types of tumors. Using spatial transcriptomics, which allows identification of different cells within different spaces, Matoso and Johnson found that macrophages (cells that can stimulate or suppress the immune system), "were significantly increased in SUC when compared with UC," says Johnson.

In further analysis, they found moderate to high levels of a protein called CD163 in SUC macrophages, suggesting that these cells may be suppressing the immune system and facilitating cancer growth. Matoso and Johnson also found that other immune system cells called fibroblasts (which support tumor growth and progression), were increased in SUC regions. "This discovery has led us to focus on targeting these two cell pathways, which may lead to further treatments to target this aggressive disease," says Johnson. This work was published in *The Journal of Pathology Clinical Research.* ■

Diabetes, Metformin, and Bladder Cancer Surgery

"We found that diabetes significantly increases the risk of developing metabolic acidosis after undergoing radical cystectomy."

A recent Brady study has identified new risk factors for a major complication in patients who undergo surgery for bladder cancer. This investigation began with the sobering fact that often, bladder cancer is not the only significant illness. "Diabetes is a common problem in this patient population," says urologic oncologist Nirmish Singla, M.D., M.Sc. Many of these individuals are also taking metformin, a diabetes-managing medication.

In a recent study, Brady investigators analyzed a national database, TriNetX, for links between having diabetes, using metformin, and developing metabolic acidosis – a serious complication in which acid builds up in the body's fluids. They examined the records of more than 13,000 patients who underwent surgical treatment for bladder cancer with a radical cystectomy and urinary diversion.

"We found that diabetes significantly increases the risk of developing metabolic acidosis after undergoing radical cystectomy," says Singla, who led the study, "especially in those who receive a continent diversion. Metformin use may also contribute to metabolic acidosis risk, but its impact may be less significant than that of diabetes itself."

For these patients, the study highlights the importance of "close management of comorbid conditions and careful attention to medications, in collaboration with a primary care or subspecialty provider," Singla adds. "We hope our findings will lead to improved outcomes and a lower risk of side effects in these patients." This work was published in *Urologic Oncology: Seminars and Investigations.* ■

DISCOVERY IN KIDNEY CANCER

Will Proton Therapy for RCC Prove Better for Long-Term Kidney Function?

"There is no one-size-fits-all therapy for localized kidney cancer," says Brady urologist Nirmish Singla, M.D., M.Sc. "Surgery is the mainstay of treatment, but it may not be an option for patients who have other serious medical conditions, or complicated tumors that are deemed inoperable."

Similarly, nonsurgical ablative therapies aren't a universal fit, either – particularly for patients with only one kidney or a large tumor very close to another organ, such as the bowel.

"Recently stereotactic body radiation therapy (SBRT), using conventional x-rays, has emerged as an effective nonsurgical option for patients with early-stage renal cell carcinoma (RCC)," says radiation oncologist Curtiland Deville, M.D., of the Johns Hopkins Proton Therapy Center at Sibley Memorial Hospital's Kimmel Cancer Center. Even so, he adds, "this can be associated with some declines in normal kidney function," because it can damage nearby normal kidney tissue.

"Proton therapy is unique in that it allows the bulk of the energy to be released at the tumor, while sparing nearby healthy tissues." This means a lower dose of energy can be used with greater effect.

Good news: In a single-arm Phase II study called SPARE, Brady investigators Deville, Singla, and Thomas Jarrett, M.D., Chief of Urology at Johns Hopkins Sibley Memorial Hospital, are studying a promising option for these patients: "Proton therapy is unique in that it allows the bulk of the radiation energy to be released directly at the tumor, while sparing nearby healthy tissues," says Deville, who serves as the Principal Investigator of the trial. This means a lower dose of energy can be used with greater effect. "We hope this will better preserve long-term kidney function." The SPARE trial (NCT06376669), supported by the Robert L. Sloan Fund for Cancer Research, is recruiting 19 patients, who will be followed for two years after treatment. ■

Deville: *"SBRT has emerged as an effective nonsurgical option for patients with early-stage RCC."*

Combination Drug Therapy in a Rare Form of Kidney Cancer

Patients with tRCC who combined two different types of therapy had a better response and better disease control.

Sometimes, genes get stuck together. They fuse to form hybrids, and the result is not good: DNA is discombobulated, abnormal proteins are produced, and cancer can result. One way this can happen is *translocation*, when a piece of DNA from one chromosome attaches itself to part of another chromosome.

This can result in translocation renal cell carcinoma (tRCC), a rare and aggressive form of kidney cancer that mainly affects women and young adults. The particular culprits in tRCC are fused transcription factor genes, most commonly *TFE3*.

Because this form of cancer is so rare, "optimal systemic treatment strategies remain unclear," says medical oncologist and Co-Director of the Kidney Cancer Research Program, Yasser Ged, M.B.B.S. "However, in small studies, immunotherapy combinations have shown promise."

Ged, along with investigators from Hopkins, Memorial Sloan Kettering Cancer Center, Fox Chase Cancer Center, and City of Hope, recently led a multicenter study of the responses of 22 patients – one of the largest studies of tRCC patients to date – with metastatic *TFE3*-positive tRCC. These patients received either dual IO therapy or IO in combination with a VEGF (vascular endothelial growth factor) tyrosine kinase inhibitor (TKI), a drug that blocks cancer from making its own supply of blood vessels.

In the study, published in the *Journal of Immunotherapy*, patients who had the IO-VEGF-TKI combination treatment had a better response and better disease control, compared to those who received the dual IO therapy. However, the authors note, larger, prospective trials are needed to confirm these findings and guide treatment strategies in this rare population. ■

Small Kidney Masses and Active Surveillance: Does Size Matter?

Larger tumor size, particularly above 2.9 cm, was associated with increased growth rate and the eventual need for treatment.

When it comes to small kidney tumors (less than 4 cm in size), discernment is everything. "As many as 30 percent of all small renal masses are benign," says Nirmish Singla, M.D., M.Sc. Director of the Kidney Cancer Program. "And among the ones that are cancerous, the vast majority either remain stable or grow very slowly and can be managed safely with active surveillance," which includes regular follow-up imaging.

Much of what doctors know about the natural history of these tumors over time comes from data collected in the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, which was founded at the Brady in 2009.

In a recent study led by Singla, Brady investigators have shed even more light on which tumors may be likely to need treatment: "We analyzed the DISSRM registry and found that larger tumor size, particularly above 2.9 cm, was associated with increased growth rate and conversion to delayed intervention for small renal masses," Singla says. "The ability to predict how these tumors will behave over time, and which tumors are likely to grow more quickly, gives us valuable information for joint decision-making with our patients in situations where there may not be a right or wrong answer." This work was published in the *British Journal of Urology International*.

Singla and colleagues also recently published the mature outcomes from the entire DISSRM registry, which includes over 950 enrolled patients, in the *Journal of Urology*. "We are proud that these data provide continued, longitudinal support for active surveillance as an appropriate strategy for small renal masses." ■

Racial and Molecular Differences in Kidney Cancers

"We found that molecular categories explained the differences better than genetic ancestry alone."

Clear-cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer – but not all cases are alike. A new Brady study has shown that there are notable differences in patients based on ancestry – and beyond this, there are distinct molecular subtypes that could affect the course of the disease and response to treatment.

In their study, published in *Cancer Research Communications*, Brady investigators compared molecular features of kidney tumors from carefully matched Black and White patients – 60 total – who underwent surgery for ccRCC. Using whole-exome sequencing and other advanced genetic techniques to look at gene mutations, and RNA sequencing to analyze gene activity, "we explored differences associated with African and European genetic ancestry," says medical oncologist Roy Elias, M.D., the study's first author.

Among the genetic alterations they looked for were mutations in *VHL*, the von Hippel-Lindau tumor suppressor gene, which helps maintain the normal functions of cells. "We found that *VHL* mutations were less common in individuals of African descent, compared to those of European descent," says the study's senior author, Nirmish Singla, M.D., M.Sc. "Additionally, tumors from patients of European descent showed higher activity in pathways linked to inflammation, cell growth, and metabolism." However, when the investigators examined the tumors at the molecular level, "we found that molecular categories explained the differences better than genetic ancestry alone."

"Our findings suggest that using molecular subtypes could improve the precision and effectiveness of therapies," says Elias. "Overall, this study emphasizes the importance of representing a broad range of patient populations in cancer research and highlights how molecular classification can lead to better, more targeted treatments for all kidney cancer patients." This work was generously supported by the Dan Hagaman Research Fund. ■

DISCOVERY IN TESTICULAR CANCER

Detecting Elusive Testicular Tumors

Clinical insight, advanced testing, and tenacity are critical in pinning down the diagnosis, especially since these tumors "respond remarkably well to chemotherapy when diagnosed and treated in time."

Diagnosing a germ cell tumor (GCT) – the most common form of testicular cancer in young men – is a mostly straightforward business, says urologic pathologist Ezra Baraban, M.D. "These tumors are usually easy to identify when they form a noticeable mass in the testicle." However, in about 12 percent of cases, GCTs are much harder to figure out – because they spread to other parts of the body without creating a telltale lump or mass. "This makes diagnosis especially challenging, and can delay life-saving treatment."

Recently, Baraban and colleagues reviewed 55 perplexing cases of elusive GCTs, "which first appeared as metastases, with spread to such distant sites as the abdomen or neck. Surprisingly, only a small minority of patients had a testicular mass at the time of diagnosis." In most cases, the tumor was first identified through a needle biopsy, "a very small sample that can be hard to interpret. We found that these needle biopsies were prone to diagnostic errors."

Not only was there not a lot of tissue to work with, says Baraban, but "more than half of the tumors also showed markers commonly seen in other cancers, which added to the confusion. As a result, only about a third of cases were correctly identified as GCTs from the start."

How can diagnosis of these tricky tumors be improved? With tenacity, as Baraban and colleagues showed, and by using increasingly specific tests. "We found that using tests for protein markers like OCT3/4 and CD30 greatly improved the chances of making the right diagnosis," Baraban explains, "but these can only be applied if one already suspects the diagnosis." In especially unusual cases, a genetic test (FISH for isochromosome 12p) also helped confirm the diagnosis. This study, published in the *American Journal of Surgical Pathology*, "emphasizes the importance of combining clinical insight, advanced testing, and a high level of suspicion when establishing the diagnosis of these metastatic germ cell tumors," Baraban says, "especially since they respond remarkably well to chemotherapy when diagnosed and treated in time." ■

Potential Biomarkers for Testicular Cancer

"We not only have uncovered novel candidate biomarkers, but potentially actionable targets to treat this disease."

MicroRNAs (mRNA) are small, noncoding RNAs that help fine-tune gene expression, and when something goes awry with these tiny genetic pieces, cancer can develop. mRNA levels in the bloodstream can be tested and, Brady research has shown, are emerging as promising and highly precise biomarkers in the diagnosis and management of testicular cancer.

Urology resident Taibo Li, M.D., Ph.D., recently led a comprehensive study to investigate the landscape of microRNA expression in testicular cancer. In the study, published in *Scientific Reports*, investigators characterized the expression profile of 2,606 microRNAs across distinct subtypes of testicular cancer, in primary tumors as well as metastatic tumor sites in the lymph nodes. They discovered new candidate microRNA biomarkers capable of distinguishing among testicular cancer types.

"These exciting findings deepen our understanding of the mechanisms of testicular cancer formation," says urologist Nirmish Singla, M.D., M.Sc. the study's senior investigator. "We not only have uncovered novel candidate biomarkers, but potentially actionable targets to treat this disease." This work was generously supported by the Ann and Chad Holliday, Jr. Discovery Fund. ■

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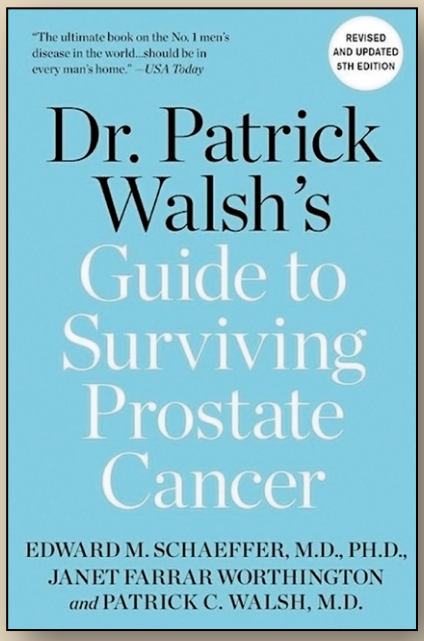

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