2017/2018

THE JOHNS HOPKINS KIMMEL CANCER CENTER

ON TARGET

The Newsmagazine of the Department of Radiation Oncology and Molecular Radiation Sciences

Honoring a Pioneer

The Moody Wharam Professorship

Moody Wharam, M.D.

Unprecedented Progress

This is an exciting time in cancer medicine, and I am privileged to share with you groundbreaking advances in radiation oncology and molecular radiation sciences. The opportunities for progress are unprecedented. Targeted therapies, immune therapies and advanced technologies, such as proton therapy and data mining, are resulting in better cancer treatments for patients and reducing the toxic side effects that have, for so long, been associated with cancer.

Radiation oncology and molecular radiation sciences has been and remains a vital part of every advance against cancer. Ongoing research continues to improve the precision, increase the strength and expand the delivery methods for radiation therapies. Research techniques—unique to the Kimmel Cancer Center—allow us to study the effects of radiation therapy in ways never before possible and to image, quantify and measure tumor responses in real time.

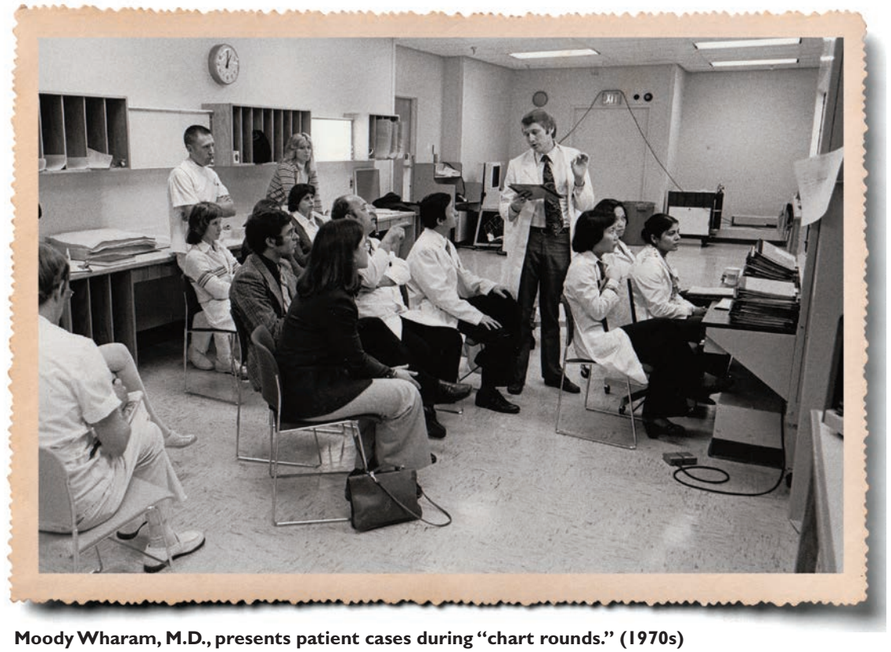
Sincerely,

Theodore DeWeese, M.D., Director
Sidney Kimmel Professor of Radiation Oncology and Molecular Radiation Sciences
Vice President for Interdisciplinary Patient Care, Johns Hopkins Medicine

Honoring a Pioneer

The Moody Wharam Professorship

Moody Wharam came to Johns Hopkins in 1975, as one of the early radiation oncologists. At that time, just 50 percent of children diagnosed with cancer survived. Cancer, and particularly pediatric cancer, was a troublesome problem, and Wharam was among a group of cancer clinicians who ushered in an era that offered the first glimmer of hope.



Moody Wharam, M.D., presents patient cases during "chart rounds." (1970s)

The National Cancer Institute appointed four study groups to investigate common childhood tumors, and Wharam received the unusual distinction and honor to be named to two of these groups. From 1980 to 1990, he served as director of the radiation oncology committee of the Pediatric Oncology Group, a U.S. and Canadian collaborative group that studied childhood cancers. His roles in these premier groups made him an active participant in all of the pivotal pediatric cancer research of the time. It was this research that led to dramatic increases in pediatric cancer survival rates.

The four separate groups have since merged into one, known as the Children's Oncology Group. The merger, Wharam says, was a marker of the success that had been made against these cancers. He could have hung is career on these impressive advances, but to Wharam, it wasn't good enough.

Taking on Toxicity

Wharam says a pediatric patient he treated for Hodgkin lymphoma highlights the paradox of these early radiation therapies in children. The patient survived the lymphoma but died of a second cancer when she was 48. "That cancer was probably caused by the treatment I gave her as a child," he says. It is a cruel irony that is particularly problematic for pediatric cancer patients. The same treatment that saves their young lives can also set into motion genetic alterations that manifest decades later as new cancers.

"Knowing that the therapies we give children for their cancers could cause other problems for them was one of the most difficult aspects of our job," says Wharam. This inspired a new mission, and Wharam became a leader of research to scale back treatment for many childhood cancers. "I had two goals," he says. "We were having great success in certain cancers, so we had to see if we could back off in the amount of radiation we were giving these patients. At the same time, kids were still dying, so we also had to figure out how we could do a better job of treating them."

In addition to the risk of second cancers decades later, radiation to growing bones and organs could impede normal development, and radiation to the brain, a common site of pediatric cancers,

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often resulted in impairments to learning and other cognitive brain functions.

Still, scaling back therapies was a risky endeavor. The primary indicator that therapy could be reined in was increased survival. Go too far in reducing treatment, and children would likely suffer deadly cancer recurrences. Few were willing to take on the challenge, but Wharam became one of the first when he collaborated with Johns Hopkins pediatric medical oncologist Brigid Leventhal in a groundbreaking study of treatment reduction in Hodgkin lymphoma. Their research led to refinements in therapy that allowed certain patients, based on specific characteristics, to receive less radiation or forgo it altogether without increased risk of recurrence.

A Special Patient

Wharam's commitment to his patients transcended every aspect of his long and accomplished career. **Theodore DeWeese, M.D.**, Director of Radiation Oncology and Molecular Radiation Sciences, was hired by Wharam. Several months ago, Wharam showed him a photo that a former patient had sent. The patient was just a toddler when the two treated him in the early 1990s for retinoblastoma, cancer of the retina, in both eyes. Now a young man, the patient stands with his parents in his college graduation robe. This patient had particular significance to DeWeese and Wharam. It was DeWeese's first patient as a resident in radiation oncology working under Wharam. It is rare to have the cancer in both eyes, and without extraordinary measures, the patient would have lost his vision. Wharam was determined to preserve the function of one eye. The only way to do that would be to deliver radiation so precisely that it would destroy the cancer without harming the anatomy of his eye.

"The treatment was so complicated that we had to do it in off hours, and Moody tasked me to come in at 6 every morning to set up for the patient," recalls DeWeese. "It required anesthesia and a special device for the patient's eye. We did this every day for weeks."

In reality, the procedure Wharam devised was stereotactic radiosurgery, a precisely targeted and technically sophisticated way to deliver high-dose radiation to cancer. This was years before advanced radiosurgery equipment had been developed.

"Moody's treatment worked, and because of his ingenuity and dedication, this patient was now graduating with an engineering degree," says DeWeese. "He would have been blind without this therapy. There are not many doctors that would have gone the extra lengths that Moody did to save this child's eye." DeWeese wondered how different that family photo might have been without their efforts decades earlier. "It shows the impact one person can have on an entire family," he says.

DeWeese says Wharam's pioneering influence earned the department the distinction as one of just a select few in the nation with a long history of expertise in treating pediatric patients.

"Moody also forged how rhabdomyosarcoma is managed in kids, and not just radiation therapy but how radiation is intertwined with chemotherapy. It remains the standard of care today," says DeWeese. Rhabdomyosarcoma is a childhood cancer of the connective tissue that attaches muscles to bones. "The way we manage children with rhabdomyosarcoma today is based on what he did through all those years of tireless work in the Pediatric Oncology Group. Kids survive this now because of the work Moody did, and that's why we do research," says DeWeese.

"MOODY'S TREATMENT WORKED, AND BECAUSE OF HIS INGENUITY AND DEDICATION, **THIS PATIENT WAS NOW GRADUATING WITH AN ENGINEERING DEGREE**. HE WOULD HAVE BEEN BLIND WITHOUT THIS THERAPY. THERE ARE NOT MANY DOCTORS THAT WOULD HAVE GONE THE EXTRA LENGTHS THAT MOODY DID TO SAVE THIS CHILD'S EYE."

– **THEODORE DEWEESE, M.D.**

This reputation of excellence was instrumental in helping the department earn approval for a proton beam facility, he says. Proton beam therapy is state-of-the-art technology that very precisely zeros in on tumors, increases the damage to cancer cells without harming normal tissue. Its precision and safety makes it desirable for treatment of pediatric tumors and particularly tumors of the brain, spine, eye, lung, head and neck, and bone. The facility, which will be located at Sibley Memorial Hospital on the Kimmel Cancer Center's National Capital Region campus, is scheduled for completion in 2019 and will include space and staff for treating pediatric patients.

"Proton beam is another major advance in managing late effects of radiation therapy," says Wharam. "It allows us to control the depth of the beam and stops it from passing through and harming critical structures like the pituitary gland and brain stem." The department's history of strength in treating pediatric cancers also led to a collaboration with Children's National Medical Center. Under the direction of pediatric radiation oncologist Stephanie Terezakis, the Kimmel Cancer Center will become the primary provider of radiation therapy, including proton therapy, to its pediatric cancer patients. The merger creates one of the largest pediatric radiation oncology programs in the country, and the increase in patient volume promises to speed clinical discovery.

A History of Innovation

Wharam's lengthy and accomplished career makes him the historian of the department and, DeWeese says, proton therapy falls in line with a constant theme among many milestones—patient-centered innovation.

In the beginning, Wharam was a member of a small team working in the basement of the Halsted Building waiting to move to state-of-the-art facilities in the new comprehensive cancer center. Wharam's work began before there was a Department of Radiation Oncology and Molecular Radiation Sciences. Computer technology was limited at the time, as were the machines that delivered radiation to patients. Like the current generation of radiation oncologists, however, Wharam and colleagues were focused on advancing clinical research and improving the standard of care for patients, albeit at a time when the technology and radiation-delivering machinery had not quite caught up with their forward-thinking ideas. "We had state-of-the-art knowledge and with the comprehensive cancer center in planning, state-of-the-art facilities were coming," says Wharam.

Radiation oncology broke off from the Department of Radiology and Radiological Sciences and joined forces with the Department of Oncology to tackle a cancer epidemic.

When the comprehensive cancer center opened in 1977, it had all of the technical aspects needed for cutting-edge radiation therapy. "We are the only specialty that makes its own medicine," says Wharam. "We retired the old cobalt machines and replaced them with linear accelerators, and we hired physicists to make sure the machines were doing what they were supposed to." Johns Hopkins was one of just a handful of strong academic programs in radiation oncology in the U.S. at the time, and Wharam recalls that when the center opened, they were immediately inundated with cancer patients. The radiation oncology clinic had to expand to twice its original size to accommodate the growing patient load. Years later, Wharam oversaw two additional expansions, one with the opening of the Kimmel Cancer Center's Harry and Jeanette Weinberg Building, and another with a satellite facility at Green Spring Station.

Wharam treated all types of cancer, but as the clinic expanded and more radiation oncologists were recruited, he made pediatric cancers his primary focus. The photographs around his office were a silent testimony to his pioneering contribution to advancing the care of children with cancer.

His face lights up when he speaks of his patients, and his detailed memories of them are remarkable. It is clear that they are his fondest memories from a long and impressive career.

The Future

Wharam retired from seeing patients in 2015. He quips that today's patients are in even better hands. "Knowing and working with some of the founders of the oncology center has brought me great joy. Those of us who were there in the beginning were right for the time, but Ted DeWeese's leadership is moving the field forward in ways we couldn't even imagine then," says Wharam. "Our program has grown into the best one in the country. We have first-class scientists and clinicians and the finest physicists, residents, nurses, radiation therapists and dosimetrists in the business. Our future is looking good."

To honor Wharam's unparalleled contribution to the field of radiation oncology and ensure this spirit of innovation and dedication continues, DeWeese initiated a campaign to establish the Moody Wharam Professorship.

"WHEN YOU THINK OF THE CHARACTERISTICS THAT MAKE A GREAT DOCTOR, **THAT IS MOODY WHARAM**—WICKEDLY SMART, TOTALLY DEDICATED, PROFESSIONAL IN EVERY INTERACTION AND KIND."

– **THEODORE DEWEESE, M.D.**

An endowed professorship is considered the highest honor in academic medicine and recognizes extraordinary talent in research, clinical care and teaching. It provides solid and sustained funding to an accomplished faculty member to support his or her continued focus on radiation oncology research and its clinical translation.

"I can't think of anymore more deserving of a professorship named in his honor," says DeWeese. "When you think of the characteristics that make a great doctor, that is Moody Wharam—wickedly smart, totally dedicated, professional in every interaction and kind. Moody has the attributes that we would all hope to aspire to."

Even in retirement, Wharam's clinical research and innovative thinking continues to influence cancer care. "This is a tangible example of how clinical research and thoughtful medicine go on well beyond what we do. Moody's work is a great example of what we do. That's about all that any one of us could hope to achieve—to have your work impact people while you are doing it and remain impactful," says DeWeese. "The Moody Wharam Professorship will continue this legacy." ■

To make a contribution or obtain more information, contact Marie-Jo Corry at 410-361-6185 or mcorry@jhu.edu.

‘Mini-Brains’ Are New Model for Brain Cancer

Tiny structures about the size of a fly’s eye provide a new futuristic opportunity to study pediatric brain cancers. These complex, organized spheres of human neural and nerve cells are dubbed organoids, or mini-brains. They cannot think or learn like a human brain, but their structure is similar enough to the anatomy of a developing brain that molecular radiation scientist **Sonia Franco**, believes they can be used to replicate how pediatric brain cancers naturally grow and spread, and to study more closely how these cancers respond to radiation and drug treatment.

It takes about three months to grow the mini-brain structures in the lab. They grow to about 4 millimeters and provide a window of four to six months for research before the cells begin to die off. Hundreds of them can be created simultaneously.

The research is in its infancy, making its way into research about four years ago. They were stumbled upon almost accidentally as Austrian researchers were growing neural stem cells, the cells that give rise to all other brain cells. The cells were placed in a rotating flask so they would form into small spheres. Checking on the cells one day, a researcher noticed a tiny black speck on her organisms and thought the cells had become contaminated. A closer look under the microscope revealed that the tiny black spot was a primitive eye.

“They had self-organized and differentiated into 3-D, brainlike structures,” says Franco. The cells took cues from their environment—a nutrient-enriched gel in a constantly rotating flask that allowed the nutrients and oxygen to get deeper into the tissue, Franco explains. It closely mimics the natural environment of how brains develop in an embryo so that cells developed into a very early version of a human brain.

Mini-brains are best known as the model used to help scientists figure out how the Zika virus causes undersized brains in the infants of infected pregnant women. Franco is the first to grow cancers in the mini-brains. Implanting tiny remnants of human brain tumors into the mini-brains will provide new insights about how tumors grow and what drugs work best against them. Ultimately, she would like to use the research model to create a precision medicine stand-in for patients.

Sonia Franco, M.D., Ph.D., and postdoctoral fellow Debamitra Das, Ph.D. Das is funded through a Catalyst Award given to organizations that recruit and advance women and diversity. Postdoctoral fellow Rajib Ghosh, Ph.D., is also a member of the research team.

Mini-brains can be created from the cells of any person. For example, researchers have the ability to coax simple skin cells to regress to their earliest form—flexible stem cells that, with the right environment, can be coaxed to develop into any type of cell. Franco envisions creating a mini-brain stand-in for a patient receiving treatment and implanting it with cells from the patient’s brain cancer. Testing drugs in the personalized model could help guide doctors toward the most effective therapies for each patient.

Franco expects the new mini-brain model to be less expensive and work better than the animal models typically used in the laboratory. “The mini-brains will show the natural physiological way cancer cells migrate and spread into the brain,” says Franco. “Animal models do not have this ability, so findings don’t translate well into the clinic.”

Franco is collaborating with neuroscientist **Vasiliki Machairaki**, radiation oncologist **Lawrence Kleinberg** and Sibley Memorial Hospital-based radiation oncologist and brain tumor expert **Matthew Ladra** to perfect her model. Ladra received funding from Children’s National Pediatric Cancer Center to explore the effects of radiation therapy on pediatric tumors and the surrounding normal brain. The joint effort is the result of a unique collaboration between pediatric oncologists and surgeons from Children’s National and radiation oncologists at the Kimmel Cancer Center to create the first dedicated pediatric radiation oncology program in the National Capital Region.

Ladra is sharing tumor samples with Franco that she can implant in her mini-brains.

“We have the potential to make mini-brains for different pediatric brain cancer types, including medulloblastoma and glioblastoma, and measure responses to drugs,” says Franco. “If we are treating a mini-brain with the same therapy the patient is receiving and it’s not working, it would alert us that we might need to change the patient’s treatment plan.”

Franco is also collaborating with radiation physicist **John Wong** who invented the Small Animal Radiation Research Platform (SARRP). It is a miniature version of human equipment and the only realistic laboratory representation of the therapy radiation oncologists provide in the clinic. Right now, it is used on animal models, but Franco and Wong believe its size offers the potential to conduct radiation research with the mini-brain model.

The mini-brain model could provide new clues about radiation resistance. Surgery followed by radiation therapy is a mainstay in children being treated for brain cancer, but brain cancers almost always come back. Franco wants to use the mini-brains to study drugs that prevent cancer cells from repairing their DNA after radiation therapy. These repairs allow cancer cells to survive. “If we give drugs before radiation treatment that prevent these repairs, radiation therapy would kill more cancer cells,” says Franco. There is also research evidence that pediatric brain cancer patients may benefit from drugs known as HDAC inhibitors. The mini-brain model could provide valuable information about how these drugs work alone and in combination with other brain cancer therapies.

“This method could really accelerate drug discovery,” says Franco. “Right now, it is difficult to get drug companies to develop and provide drugs for pediatric cancer. Using such a humanlike model could provide convincing results about the effectiveness and toxicity to brain cells needed to get drug companies on board.” ■

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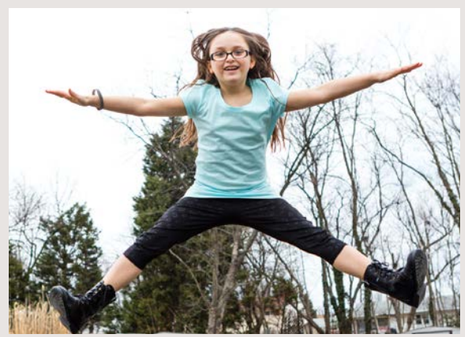
RILEY, 11, has a slow-growing and rare benign brain tumor called a pylocytic astrocytoma. She calls her tumor Roger and says, “I kicked his butt.” The tumor, located between her optic nerve and pituitary gland, can’t be taken out surgically, and will require lifelong monitoring with drug therapy and radiation therapy, when she is older, to keep it from growing into her optic nerve and affecting her vision. This is an example of the kinds of tumors Franco’s mini-brain model could impact, providing new information about how they grow and the therapies that may work best.



Using Data to Improve Patient Care

The era of precision or personalized cancer medicine is driven by data, and many experts believe that the solutions to a lot of the remaining cancer mysteries may be hidden within this data. Radiation oncology physicist **Todd McNutt** is among them. Within a sea of data, the challenges are figuring out what information has the value to advance patient care and how to extract it.

"There are so much more data collected than is ever used," says McNutt. To put some of this unused data to work in radiation therapy, he built—from the ground up—a complex, computerized data mining system. It is called Oncospace, and it scrutinizes and analyzes data from prior patients who received radiation treatment to improve the treatment of new patients. It evaluates the therapies that worked best for a particular cancer as well as those that resulted in less than favorable outcomes and generates an optimal treatment plan.

Creating this complex, interactive system has been a laborious, 10-year process for McNutt and colleagues, but it is rapidly gaining traction in the research and clinical settings. "The practice of cancer medicine naturally creates data," he says, "but for the first time in history, we have the technology to sift and sort through these data in completely new ways."

"Todd has proven that large data warehouses of patient information collected from previously treated patients can be used to individualize treatment decisions for new patients," says **Theodore DeWeese**, Director of Radiation Oncology and Molecular Radiation Sciences.

Oncospace does more than collect and store data. It takes informatics to the critical next level with the capability to perform interactive analysis that informs clinical decision-making. Radiation oncologist and head and neck cancer expert **Harry Quon** put the system McNutt designed to the test in clinical practice.

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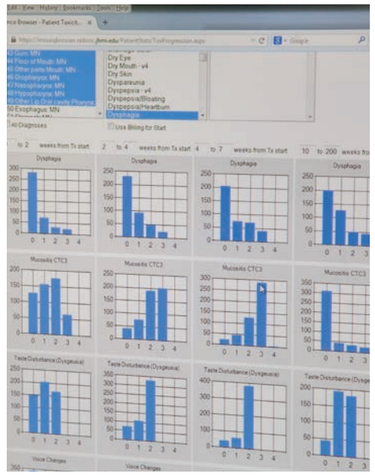
In working with radiation, the line between healing and harming is almost as narrow as the beam itself. Quon understands the consequences of crossing that line. His job is to develop the treatment plans that use radiation to destroy cancers in the head and neck without causing permanent damage to the dense anatomy surrounding the cancer. Patients want their disease cured. They do not want to be left unable to speak or eat, but these are some of toxic effects radiation treatment of head and neck cancers can cause.

This was also the reason McNutt saw these cancers as the ideal choice to put Oncospace to the test. Head and neck cancers are among the most difficult cancers for radiation physicists and oncologists to plan for, often requiring as many as 20 treatment revisions as they work to design a treatment that hits the cancer with radiation but does not do damage to vital organs and glands, such as the voice box and salivary glands.

McNutt's system provides the guidance that allows Quon and other clinicians to maximize the healing and minimize harm. It scours all of the data on head and neck cancer patients treated in the Kimmel Cancer Center; charts radiation dose distributions, toxicity and other data in vividly colored computerized maps and graphs; and reveals the optimal plan. At the same time, it takes into account and connects all of the variables—age, underlying health conditions and other treatments patients are receiving—and figures out how all of these variables relate and influence toxicities and response to treatment. "We can build predictive models of toxicities and other side effects based on data we have collected from prior patients, including indicators that a patient may be at higher risk for certain treatment toxicities, and use this information to adjust the treatment plan," explains McNutt.



Big data is the next medical frontier.

"There is knowledge in the variations in toxicities and response that occur from patient to patient," says Quon. "That type of analysis is not possible without the analytic capabilities of Oncospace. It does what no other tool can do and allows us to see unique relationships that otherwise would be hidden."

As important as the data it stores and analyzes is the interface it uses to gather the data. McNutt worked closely with Quon and other members of the clinical care team, including nurses, speech pathologists and nutritionists—all of the specialists involved in the treatment of head and neck cancer patients—to develop web-based assessment forms so that all of the information collected by caregivers could be easily integrated into the clinical workflow and ultimately into the Oncospace database. "It requires some changes in habits and doing things a little bit differently than we were used to, but the reward gets people on board," says Quon. "We have a tool that no one else has. As a result, we've improved our patient care and doubled our head and neck practice."

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– HARRY QUON, M.D.

McNutt and Quon have proven that Oncospace improves treatment plan quality and reduces toxicities. Now they are using it to track and improve treatment outcomes and to advance research. McNutt says it is imperative that the data be tied to outcome, and he is among the first to take on the challenge.

More recently, they earned a grant from information technology giant Toshiba to incorporate imaging into the data collected.

The grant is playing a major role in providing funding and scientific expertise to help McNutt and team adapt the Oncospace system to incorporate data, including imaging, on disease response and status: Is the cancer stable? Has it progressed? Did it recur? Toshiba has developed a sensor system for computers that generates millions of data points on temperature, usage and other factors to provide predictive models for hard drive failure. McNutt is hopeful that this data mining expertise can be applied to cancer medicine through Oncospace.

Some of the new data he hopes to use to enrich Oncospace are in CT imaging scans done in treatment simulation to guide how patients are positioned. These images are not currently used beyond that purpose, but inherent in these scans is information that shows how tumors are responding to treatment. If the scans could be incorporated automatically into Oncospace, it would allow them to track the history of the tumor during treatment. "Using Oncospace to analyze and quantify these daily images, we could potentially tell early on in the course of the treatment if the tumor is responding and change the treatment plan if necessary," says McNutt. He says it is the radiation oncology version of the work being done in molecular genetics using genetic biomarkers to track and monitor the response of cancers to targeted drug therapies. "It is real-time, in-treatment monitoring," says McNutt. "The same way we used the system to relate the dose of radiation to the parotid salivary gland to the loss of gland function, we can use it to relate treatment plans to treatment responses."

McNutt also hopes to gather notes in text from treating physicians. This is a bigger challenge because text is not the language of computers, and for that reason, he says, many data mining systems are missing this critical clinical piece. "Physicians are trained to document records for communication, but not for data collection," says McNutt. To incorporate patient outcomes in Oncospace, McNutt worked with clinicians to develop a new interface designed to extrapolate clinical information through a numerical ranking system caregivers use each time they see a patient.

As McNutt continues to expand the capabilities of the pioneering system he built, its success in head and neck cancer has made it the model for use in other cancer types, including lung, pancreatic and prostate cancers. He is also planning to extend the use of Oncospace to other cancer centers in a novel endeavor that has never before been tried but offers to even more extensively realize the power of data. If the answers are in the data, than more data analyzed should lead to more rapid discovery of better road maps for care. Partner institutions would be given access to Oncospace technology and share their results with all of the other participating centers. McNutt says sharing the technology with other institutions will also allow many cancer types to be studied simultaneously. ■

Novel Finding Improves Cancer Cell Death

An unusual observation by Johns Hopkins scientists about how testosterone affects prostate cancer cells may lead to more effective radiation therapy in men with high-risk disease.

Currently, the standard of care for men with prostate cancer that is likely to recur or spread beyond the prostate is to combine hormonal therapy with radiation therapy—a powerful approach that has been shown to improve control of cancer in the pelvis, reduce the likelihood of metastasis, and prolong life.

"Typically, we treat men with hormonal therapy for two months, followed by radiation plus hormonal therapy," says **Theodore DeWeese**, director of the Department of Radiation Oncology and Molecular Radiation Science. "In some men, the hormonal therapy continues for 24 months after the radiation. Despite this, some 30 to 50 percent of men still have a recurrence of their high-risk cancer. New approaches to improve these outcomes are critically needed."

DeWeese, with research scientist **Vasan Yegnasubramanian**, and their team, may have found a better way to control the cancer. "Recently, some members of our team found that testosterone stimulation of prostate cancer cells can result in breaks of the DNA," says DeWeese. "This was a novel finding, and in some ways, it's very similar to what we already knew about how radiation also causes breaks in DNA." Putting the two ideas together led DeWeese and Yegnasubramanian to wonder whether they could take advantage of this. Could they coordinate hormonal therapy and radiation in a way that could exploit the DNA breaks and achieve better results?

"We believe our results may have significant implications for altering current clinical management of men with high-risk prostate cancer.

Theodore DeWeese, M.D., with nurse Nicole Mills

"These data led us to consider," DeWeese adds, "that testosterone stimulation after an initial period of testosterone deprivation, when appropriately timed with radiation therapy, might lead to particularly effective control of high-risk prostate cancer—a radical notion that, if proven, would represent a paradigm shift for treatment of high-risk prostate cancer."

DeWeese and Yegnasubramanian began to explore this possibility in the laboratory. First, their team treated human prostate cancer cells growing in a dish with testosterone and radiation. They found that "indeed, the combination of the two treatments resulted in more harmful breaks to the DNA than either one alone." But did the extra DNA damage kill more cancer cells? To answer this question, they treated mice with human prostate tumors "in the same way we treat men with prostate cancer," DeWeese explains. "That is, we first reduced their testosterone level, then delivered radiation to their tumors while the testosterone levels were still low." Just as it does in humans, this treatment helped control the growth of aggressive prostate tumors. But some of the tumors regrew quickly. Next, they tried their alternate timing strategy with testosterone and radiation. "In this experiment, we deprived mice of their testosterone, and once the testosterone was very low, we gave testosterone back to the mice and then irradiated the tumors. As we hypothesized, the mice treated in this way had tumors that were far better controlled than with the standard treatment."

These results suggest that treating prostate tumors with radiation while a jolt of testosterone simultaneously breaks the cancer's DNA provides better tumor control. "We believe our results may have significant implications for altering current clinical management of men with high-risk prostate cancer," says DeWeese. The next step is to determine the best timing and radiation dosage.

A test to determine if the treatment is working is currently being developed. "When cancer cells are killed by radiation therapy, the amount of cancer DNA should decrease. Measuring this DNA in blood or urine samples will tell if cancer cells are dying off," says DeWeese. ■

"WE BELIEVE OUR RESULTS MAY HAVE **SIGNIFICANT IMPLICATIONS** FOR ALTERING CURRENT CLINICAL MANAGEMENT OF MEN WITH HIGH-RISK PROSTATE CANCER." **–THEODORE DEWEESE, M.D.**

An Unexpected Cancer Target

"When we think about radiation therapy, it is high technology, but the complexity of cancer requires that we have a better understanding of the biology," says **Marikki Laiho**, the Willard and Lillian Hackerman Professor of Radiation Oncology and Vice Chair of Research. "Now, we combine technology with biology, and that ultimately means improved treatments for patients."

This biological underpinning led Laiho to an exciting discovery that appears to stop cancer cells in their tracks. She identified an unexpected target for cancer therapy and developed a drug that hits the target.

Marikki Laiho, M.D., Ph.D.

The drug goes after a kind of cellular machinery called the RNA polymerase 1, or POL 1. Our DNA is read by RNA polymerases. Cells have three main ways—polymerase (POL) 1, 2 and 3—to read the instruction manual that is our DNA and convert the instructions into actions that are carried out by genes. Errors in the genetic code, known as mutations, alter how proteins are read and ultimately how cells behave. POL2 is studied most in cancer because it executes the primary program for reading the major cancer mutations identified to date. The other two polymerases provide tools to help translate our DNA into actions carried out by proteins.

"POL1 is fundamentally important for every cell, so it has not been considered an actionable target for cancer therapy. If you hit it, the thought was that you would harm every cell, not just cancer cells," says Laiho.

Laiho proved that was not the case after developing a drug that targets POL1 and studying it in the laboratory. She found that cancer cells rely on it more than normal cells, so it was possible to interfere with the pathway without causing excessive damage to normal cells. "Cancer cells can't survive without this program. They can't function," says Laiho. "Just as important, however, normal cells don't take much notice."

She has spent the last three years deciphering how POL1 works and developing tools to measure its activity in cancer cells. Working with prostate cancer expert and pathologist **Angelo De Marzo**, Laiho used these tools, and a large Challenge Award from the Prostate Cancer Foundation, to develop a test that identifies prostate cancers that rely on POL1. This was the first step to a clinical approach.

Laiho discovered a drug called BMH-21 by looking through a library of existing drugs. Then she and her team identified the POL1 target. Now Laiho is working with Johns Hopkins medicinal chemist James Barrow to refine it. She was surprised by how well the drug worked in preclinical proof-of-principle studies. "Without this transcription machinery, cancer cells couldn't recover," says Laiho. "They cannot function."

BMH-21showed exceptional activity against cancer cells from many tumor types. In fact, in these studies, the drug functioned better against the cancer cells than many FDA-approved cancer drugs. "We have been able to confirm that BMH-21 works by binding to DNA and are very near the optimal stage of drug development," says Laiho. "Typically, many revisions to the lead molecule are required before it is ready for clinical studies. We are very excited because that is not the case with our drug, and that means we are closer to the clinic than we could have ever imagined."

With most of the science in place, the research could be translated into a new treatment in a little over a year. Still, Laiho and team face some hurdles. She needs funding and a pharmaceutical partner to make the leap from laboratory to clinic, and since POL1 is an unusual cancer target, it has been difficult for Laiho to get pharma interested in the new drug. A prestigious Harrington Discovery Institute Scholars-Innovator Award, the Patrick C. Walsh Prostate Cancer Research Fund and the Allegheny Health Network are providing much-needed funding to move her closer to that goal.

Perhaps the most exciting element of Laiho's discovery lies in its application across many cancer types. "Even though we are looking at prostate cancer and melanoma now, BMH-21 appears to work in many solid tumors with high dependency on the POL1 pathway," says Laiho. "The more a tumor depends on this pathway, the better this treatment should work." She hopes to be able to obtain enough support to soon launch clinical trials in prostate cancer patients who have exhausted all other treatment options and to make the necessary modifications to BMH-21 to expand studies to other cancers. ■

New Drugs Improve Kill Effect of Radiation Therapy

Cancer cells are crafty—just ask clinician-scientist **Phuoc Tran**. In his current research, he has seen how cancer co-opts an exquisite process of human development to undergo its most lethal transformation. A process that normally directs an embryo to grow from a single cell into a fully developed human being may be the same one used by cancer cells to invade other parts of the body.

"IT IS METASTATIC DISEASE THAT PATIENTS ARE DYING FROM, AND **DECIPHERING EMT COULD BE AN IMPORTANT STEP** TOWARD HELPING THESE PATIENTS."
– PHUOC TRAN. M.D., PH.D.

This cellular guidance program is called EMT, and Tran says a cell undergoing EMT to form an embryo looks exactly the same as a rogue cancer cell as it spreads from its place of origin to a different organ in the body.

"The program isn't bad, but the timing is," explains Tran. The downstream consequences of this bad timing are the most critical event in the timeline of a cancer development, a sentinel event that often distinguishes a curable cancer from an incurable one. It is called metastasis, and it occurs when a cancer migrates to another part of the body. This is the stage that ups the ante because it usually causes cancers to become resistant to treatment.

Stopping or reversing the event is a priority of Tran's. "Local disease is often curable with standard therapies," he says. "It is metastatic disease that patients are dying from, and deciphering EMT could be an important step toward helping these patients."

EMT is a program that should be turned off and filed away after full embryo development. What reactivates it is not completely understood, but Tran suspects it is an ongoing injury to cells, such as chronic inflammation. "Cancer cells select the processes they need to survive. They don't reinvent the wheel. Everything cancer needs is already there," says Tran. "It pulls the programs it needs from our DNA and uses them to its advantage." What's more, there is a natural cellular resistance built in to EMT. It's an important safeguard that allows embryos to grow and survive, but in cancer, this resiliency makes for a resistant cancer. "A spreading cancer is like an astronaut going into space. He has special equipment to adapt and survive in a foreign environment. EMT provides survival gear to cancer cells, allowing them to travel and invade distant parts of the body, and resist external stimuli that would kill normal cells," says Tran.

To prove his theory, Tran is using a uniquely engineered mouse model that allows him to turn genes on and off. By manipulating genes, he is able to make the mice get spontaneous tumors in different organs, creating an animal research model representative of the way humans develop cancers. With this realistic model, Tran can study the role of EMT in many cancer types. By incorporating luciferase, the gene in fireflies that causes their iconic glow, into the model, Tran and team are able to make all of the genes related to EMT glow in the mice.

He has identified a plant-based drug called harmine that directly interferes with the EMT program. Now, he can test the drug in his unique animal model and other laboratory models to see if it can block EMT, and convert resistant cancers to radiation treatment and anticancer drug-responsive cancers.

EMT is not Tran's only focus, however. As a radiation oncologist, he is always searching for new ways to make cancers more sensitive to radiation therapy.

He believes he may have found one in the DDX3 gene. It is common across cancers, and if it is taken away, the cancer cannot survive.

Tran is collaborating with radiology and radiological science researcher **Venu Raman**, whose homegrown drug RK33 targets DDX3 and inhibits cancer cell growth and also their ability to repair DNA damage caused by radiation therapy. Tran is testing the effectiveness of the drug using his engineered mouse model and the Small Animal Radiation Research Platform, invented by radiation physicist John Wong. Early promising data mean the drug may be moving closer to the clinic.

The drug appears to have broad activity, already showing promise in sarcoma and lung, breast, prostate, brain and colon cancers. Tran says the next step is to gain investigational new drug approval from the FDA and funding to move the drug to clinical trials. ■

New Tool Delivers Prostate Cancer Destruction

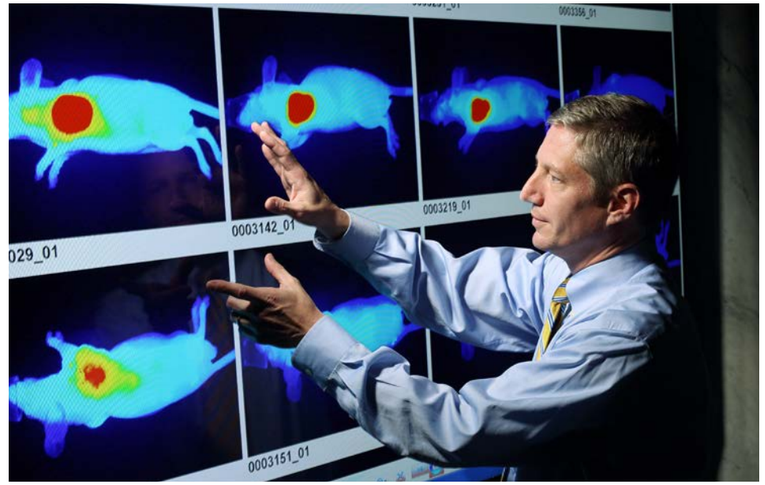
The merging of two discoveries provides a novel way to deliver cell destruction to prostate cancer. At the center of the research are two things familiar only to scientists—aptamers and siRNA.

Aptamers are small molecules that work much like antibodies to target things—like cancer—that don't belong in our bodies. They are really good at binding to other molecules. Prostate cancer expert **Shawn Lupold**, developed an aptamer that targets the prostate-specific membrane antigen (PSMA), a protein found in most prostate cancer cells.

Today, the process is automated, and Lupold can make his aptamer in two weeks, but when he first took on the project as a graduate student, it took him five years to drill down to just the right chemical formulation among many billions of molecules.

At the same time Lupold was working on his aptamer, **Theodore DeWeese**, Director of Radiation Oncology and Molecular Radiation Sciences, was working on another technology called small interfering RNAs (siRNA), which have the ability to turn off genes. Radiation therapy kills cancer cells by damaging their DNA. Some cancer cells, however, are able to repair the damage and survive, so DeWeese's plan was to use siRNA to turn off genes that help perform these repairs. Lupold's aptamer would allow him to do it selectively—causing harm only to cancer cells.

Lupold's prostate cancer-targeted aptamer was the perfect delivery vehicle for DeWeese's radiation-sensitizing siRNAs. Their final product was an aptamer that used PSMA as a chemical GPS system to guide the siRNA to prostate cancer cells where they block DNA repair mechanisms, making prostate cancer cells ultrasensitive to radiation therapy.



Shawn Lupold, Ph.D.

"It's almost as if we turned up the radiation, but we did it molecularly," says Lupold. Actually increasing the dose of radiation therapy would surely kill more cancer cells but be far too toxic to normal cells. This approach has the same effect and is safe.

Their treatment worked well in animal models, and aptamers are already FDA-approved for other medical purposes, so Lupold and DeWeese do not anticipate any safety problems. To move the therapy to clinical trials, they will need about $1 million to outsource the production of clinical-grade aptamers.

Lupold and DeWeese are also exploring aptamers as a way to safely deliver and track radiation-releasing alpha particles to painful and deadly prostate cancer cells that spread to the bone.

DeWeese says the cancer-targeting siRNA aptamers are unique to Johns Hopkins and considered the gold standard. The current version is specifically targeted to prostate cancer, but he says with an adjustment to the chemical GPS, they can be adapted to target essentially any cancer. ■

"IT'S ALMOST AS IF WE TURNED UP THE RADIATION, BUT WE DID IT MOLECULARLY. IT HAS THE SAME EFFECT AS INCREASING THE DOSE OF RADIATION—**KILLING MORE CANCER CELLS**—BUT WITHOUT TOXIC SIDE EFFECTS TO NORMAL CELLS." **– SHAWN LUPOLD, PH.D.**

Combined Radiation/ Immune Therapies

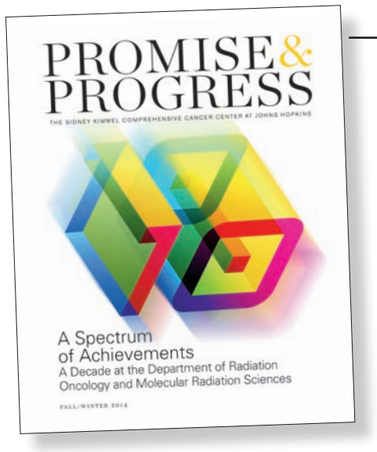
Experts from the Department of Radiation Oncology and Molecular Radiation Sciences are expanding evidence that shows targeted radiation stimulates an immune response against cancer.

As cancer cells are destroyed by radiation, they release their proteins into the bloodstream, clearly revealing their identities as cancer cells and, as a result, attracting the attention of the immune system. Conversely, however, there is growing proof that limiting radiation therapy to certain areas may also benefit the immune response to cancer.

Radiation oncology resident **Ariel Marciscano** is collaborating with experts in the Bloomberg~Kimmel Institute for Cancer Immunotherapy to study how best to treat lymph nodes surrounding tumors that potentially may harbor hidden cancer cells. Radiation therapy is typically administered to these lymph nodes, but Marciscano has found it may destroy certain white blood cells that live in the lymph nodes and are critical to the immune response.

Using the small animal radiation research platform (SARRP), invented by radiation physicist **John Wong**, Marciscano compared mouse models radiating only the tumor to models radiating the tumor and lymph nodes. His findings, featured at the annual meeting of American Society for Radiation Oncology, showed that treatment of the lymph nodes might hinder the immune response to cancer. Marciscano's research, made possible by SAARP technology, is the first of its kind and indicates a need to shift the treatment paradigm when radiation therapy is combined with immunotherapies. Learning how to administer and sequence combined treatments involving immunotherapies is critical to their effectiveness, and this study provides vital new information essential to advancing emerging immune-targeted therapies.

Ariel Marciscano, M.D.



Radiation Oncology on the Web

Read in-depth stories about research and clinical progress from the Department of Radiation Oncology and Molecular Radiation Sciences at http://bit.ly/RadOncPP

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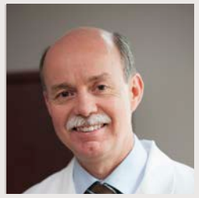


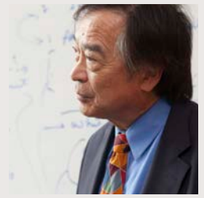
Theodore DeWeese, M.D., the Sidney Kimmel Professor and Director of Radiation Oncology and Molecular Radiation Sciences, was named vice president of interdisciplinary patient care for Johns Hopkins Medicine. He will work with other directors to develop new service lines across the Johns Hopkins system, and will build on the work he helped catalyze to form the highly successful Kimmel Cancer Center multidisciplinary clinics.

Matthew Ladra, M.D., M.P.H., assistant professor of Radiation Oncology and Molecular Radiation Sciences, was named one of *Washingtonian* magazine's 40 Under 40. The honor highlights men and women under age 40 who are "shaping local industries." The magazine calls the winners "names you should know now—because they'll be part of the conversation for years to come." Ladra was selected for running the Kimmel Cancer Center at Sibley pediatric radiation oncology program, a collaborative program with the Children's National Health System that provides radiation oncology experts and greater convenience for families who live in the national capital region.

Marikki Laiho, M.D., Ph.D., the Willard and Lillian Hackerman Professor of Radiation Oncology and Vice Chair of Research, received the prestigious Harrington Discovery Institute Scholars-Innovator Award. Laiho was chosen for her research on the RNA polymerase pathway, called POL1. It is a critical pathway mutant cancer genes use to communicate with cancer cells and recover from damage caused by radiation treatment. Laiho developed a new compound, known as BMH-21, that disrupts this communication, causing the death of cancer cells.

Ana Kiess, M.D., Ph.D., received the *Journal of Nuclear Medicine*'s Editor's Choice Award for her paper on PSMA-targeted α-particle radiopharmaceutical therapy, a new prostate cancer-targeted treatment that delivers radiation-releasing alpha particles to cancer cells that have spread throughout the body. The article also highlights the importance of micro-scale dosimetry studies to measure and better understand the amount of radiation the body receives. The journal selected the paper as one of 2016's top three basic science manuscripts.

Phuoc Tran, M.D., Ph.D., was appointed clinical director of radiation oncology. Tran also received a $1 million Movember-Prostate Cancer Foundation Challenge Award to study stereotactic radiation therapy as an immune-stimulating approach to advanced prostate cancer. In 2015, he was also selected for the ASCO Leadership Development Program. Tran's research includes a new approach to salvage radiotherapy for prostate cancer, a mainstay of treatment for men with a persistently detectable PSA or a delayed rise in PSA without evidence of cancer spread. Salvage radiotherapy alone does not always control PSA progression for men at highest risk for prostate cancer progression. Tran is studying whether adding drugs that target the androgen, or male hormone, receptors to salvage radiation therapy will better control prostate cancer and prevent cancer recurrence.



John Wong, Ph.D., director of medical physics, received two prestigious honors. He was awarded the 2017 Edith Quimby Lifetime Achievement Award of the American Association of Physicists in Medicine. In addition, the first conceptual paper on adaptive radiation therapy in *Physics in Medicine and Biology*, co-authored by Wong, was selected as one of the journal's 25 most important papers published in its 60-year history. The paper was featured in the journal's 60th anniversary collection and was among the papers celebrated at the 50th anniversary of the International Conference on the Use of Computers in Radiotherapy.

Milestones

from the Department of Radiation Oncology and Molecular Radiation Sciences

2003

The Department of Radiation Oncology and Molecular Radiation Sciences was established.

2004

IMRT (Intensity Modulated Radiation Therapy) Program began to deliver high-precision radiation that conforms to the three dimensional shapes of tumors, and delivers higher and well-defined doses of radiation to tumors, and even specific areas within tumors, while minimizing radiation to surrounding normal tissue.

2005

Physicist John Wong, Ph.D., pioneered new radiation treatment research methods and models. Wong constructed miniature versions of the equipment used to treat patients to perform never-before-done animal research models. These models allow researchers to study the best ways to target radiation-based treatments to tumors and, at the same time, prevent damage to normal cells.

2006

Research by Director Ted DeWeese, M.D., revealed that lower doses of radiation may kill more cancer cells by eluding a protein called ATM, a damage detection mechanism for cancer cells. Researchers are now exploring whether using a drug to block ATM could trick cancer cells into ignoring the damage signals so that radiation effectively destroys more cancer cells.

2007

The stereotactic body radiation therapy program began. This knifeless surgery uses highly focused beams of radiation to ablate tumors.

2008

Molecular Radiation Sciences research accelerated under the leadership of Marikki Laiho, M.D., Ph.D., who began to decipher the biology of DNA damage response to radiation therapy and how cells sense and repair this damage.

2009

Faculty Advisor Danny Song, M.D., developed a computer-assisted version of brachytherapy, a prostate cancer therapy that uses radioactive seeds inserted in the prostate to kill cancer cells. The innovation allows for more precise placement of seeds. An even more precise version followed, using an MRI-assisted robotic needle to accurately insert the seeds.

2010

An international team of collaborators led by Marikki Laiho, M.D., Ph.D., the Willard and Lillian Hackerman Professor of Radiation Oncology, developed a technique to keep normal and cancerous tissue surgically removed from the prostate alive and functioning for up to a week. This research, which allows investigators to test anticancer drugs on live tissue, is helping experts better understand the biology of prostate cancer and speeding the development of personalized therapies.

2011

Pediatric radiation oncologist Stephanie Terezakis, M.D., led the first-ever in-depth, scientifically based safety analysis of radiation oncology and reported that a combination of several well-known safety procedures could greatly reduce patient-harming errors in the use of radiation to treat cancer. She and collaborators determined that a combination of approximately six common quality assurance (QA) measures would have prevented more than 90 percent of the potential incidents.

2012

Physician-scientist Phuoc Tran, M.D., Ph.D., deciphered the relationship between a cancer growth-promoting gene called c-Myc and the ability of cholesterol-lowering drugs called statins to decrease the risk of advanced prostate cancer. In laboratory studies, Tran showed that high-dose statins reduce c-Myc activity.

2013

Marikki Laiho, M.D., Ph.D., uncovered a potential way to stop cancer cells in their tracks. The research focuses on the RNA polymerase pathway, POL1, which is necessary for mutant cancer genes to communicate with cells. In studies using human cancer cell lines, a new, never-described compound known as BMH-21 destroyed this critical communication pathway. These early studies hold great promise because without this transcription machinery, cancer cells cannot recover or function.

2014

In an interdisciplinary research collaboration, Theodore DeWeese, M.D., and colleagues revealed that testosterone, a hormone prostate cancer cells need to survive, can also form breaks in the DNA that would make cancer cells more vulnerable to treatment with radiation therapy. The researchers are studying whether short pulses of testosterone, enough to stimulate the breaks but not so much to stimulate the cancer, followed by radiation therapy may cause even more DNA breaks to overwhelm and kill prostate cancer cells.

2015

A unique collaboration between our department of Radiation Oncology at Sibley and Children's National Pediatric Cancer Center resulted in the first dedicated pediatric radiation oncology program in the National Capital Region. It brings together pediatric medical and surgical oncology experts from Children's National Health System and pediatric radiation oncology experts from the Kimmel Cancer Center to provide comprehensive pediatric cancer care, including clinical trials, to patients in the region.

2016

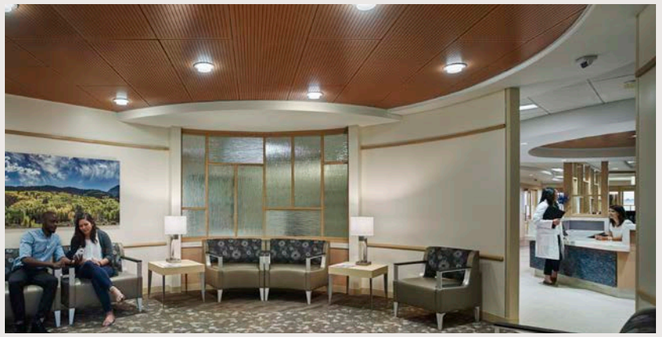
The Sidney Kimmel Cancer Center at Sibley Memorial Hospital opened in August, adding medical oncology and surgical oncology to the already established and growing Radiation Oncology Program. The 36,000-square-foot facility brings patients the most advanced radiation therapy technologies, latest techniques and innovative treatments—the same techniques and technologies used throughout the Johns Hopkins Kimmel Cancer Center.

2017

Akila Viswanathan, M.D., M.P.H., executive vice chair, professor and director of radiation oncology services for the National Capital Region campus, and director of gynecological radiation oncology services for Johns Hopkins, brought a pioneering new therapy to the Kimmel Cancer Center. Viswanathan, considered the pre-eminent expert in gynecologic radiation therapies, developed MRI-guided brachytherapy for cervical cancer and other gynecologic cancers. Johns Hopkins has pledged to continue this one-of-a-kind therapy in her new position.

Kimmel Cancer Center at Sibley Opens

The Sidney Kimmel Cancer Center at Sibley Memorial Hospital opened in August adding medical oncology and surgical oncology to the already established and growing Radiation Oncology Program. The 36,000 square foot facility brings patients the most advanced radiation therapy technologies, latest techniques and innovative treatments—the same techniques and technologies used throughout the Johns Hopkins Kimmel Cancer Center.

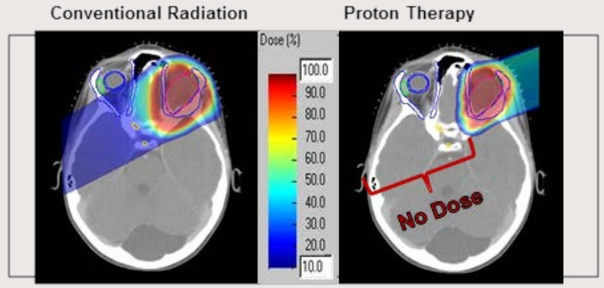


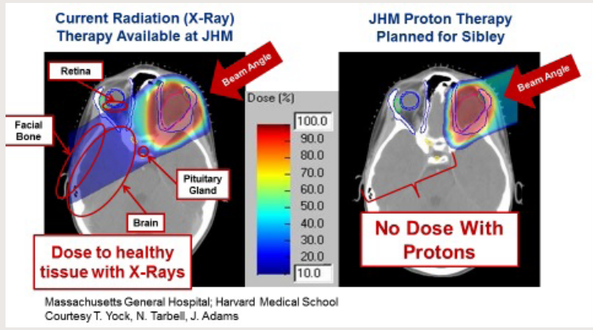
The Johns Hopkins National Proton Therapy Center at Sibley Memorial Hospital

Johns Hopkins will open one of only 20 proton therapy centers in the nation at Sibley. Construction of an 80,000-square-foot proton facility is currently underway and expected to be completed in 2019. The Johns Hopkins facility will be the most state-of-the-art available in the United States.

Proton therapy is a form of targeted radiation treatment that very precisely zeros in on tumors, increasing the damage to cancer cells while minimizing radiation exposure and damage to healthy tissue and organs. This is particularly important in the treatment of children, who often suffer lasting side effects from toxic cancer treatments. Because of its precision, proton therapy makes it possible to treat cancers near delicate organs, such as the spinal cord and heart, and offers a new treatment approach for recurrent cancers. Proton therapy provides an effective and safe way to treat cancers that present a challenge because of their location in the body, such as brain cancer and cancers in the brain, eye, base of the skull and neck.

"Proton therapy will amplify our ability to provide the most advanced care to all patients, from children to the elderly, and allow us to extend this care to more patients through partnership with our collaborators," says **Akila Viswanathan, M.D., M.P.H.,** National Capital Region Director of Radiation Oncology and Molecular Radiation Sciences.





A New Pediatric Cancer Collaboration

A unique collaboration between our department of Radiation Oncology at Sibley and Children's National Pediatric Cancer Center resulted in the first dedicated pediatric radiation oncology program in the National Capital Region. The collaboration began in July 2016 and brings together pediatric medical and surgical oncology experts from Children's National Health System and pediatric radiation oncology experts from the Kimmel Cancer Center to provide comprehensive pediatric cancer care, including clinical trials, to patients in the region.

THE JOHNS HOPKINS KIMMEL CANCER CENTER

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