THE JOHNS HOPKINS KIMMEL CANCER CENTER

ON TARGET

THE NEWSMAGAZINE OF THE **DEPARTMENT OF RADIATION ONCOLOGY AND MOLECULAR RADIATION SCIENCES**

The Precision of Proton Therapy

Care. Collaborate. Create.

2021-2022

PROTON THERAPY

Announcing the Latest Advances in Care as we Collaborate to Create the Region's Best Proton Therapy Center

CARING ABOUT OUR patients is our top priority. Combining advanced technology with compassionate care is the hallmark of Johns Hopkins Medicine. Innovations beyond standard technology set us apart from a routine experience. These innovations are the result of the unsurpassed level of expertise in radiation oncology, molecular radiation sciences, physics, surgical oncology, medical oncology, cancer biology, engineering, quantitative sciences and more that Johns Hopkins Medicine and the Johns Hopkins Kimmel Cancer Center bring to proton therapy. This level of knowledge and multispecialty collaboration is fundamentally what sets the Johns Hopkins Proton Therapy Center apart from most other proton centers across the U.S. Expertise matters because the real value of the proton beam is in the specialists who develop it and use it.

Proton therapy is a rare commodity, with less than 40 centers in the U.S. The level of care, collaboration and innovation that the Johns Hopkins Proton Therapy Center brings to this treatment is even rarer. The Proton Therapy Center is among the very few that will combine cancer treatment excellence across all disciplines with proton therapy excellence.

Building upon a lengthy history and strong foundation of pioneering discoveries in radiation therapy, this center has the technology to deliver the most advanced and patient-centered care. The translational ingenuity that merges laboratory discovery with clinical care thrives in the Kimmel Cancer Center. It was engaged throughout the planning and construction of our proton center. As a result, it is one of the most comprehensive in the world, one of the very few with dedicated proton beams for research and a specialized pediatric team.

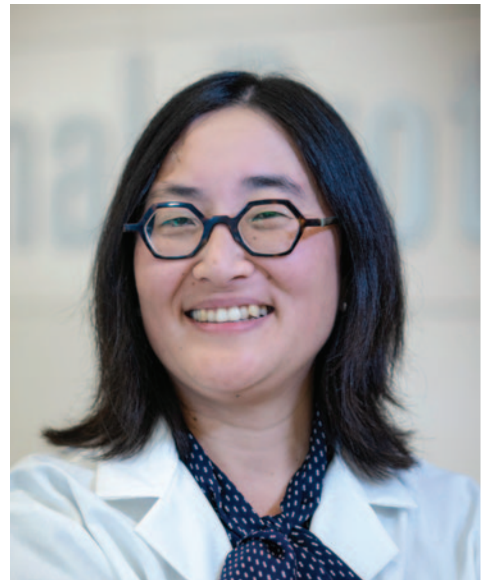
Proton therapy is not new, and the science is far from settled. "Although it has been around for a long time, it is very much in its infancy in terms of research and potential," says **Akila Viswanathan**, M.D., M.P.H., Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

As a result, what truly is new in proton therapy is what the Johns Hopkins Proton Therapy Center brings: the laboratory and clinical research to make it better and to advance its use as a tool of precision medicine. Our proton therapy center is among a select few academic centers in the country — and the only in the region — doing research to determine in which situations this type of radiation treatment is the best option.

"Proton therapy is an incredibly complex and precise tool, and there is still much to be done for experts to harness it full potential," says **Christina Tsien**, M.D., brain tumor expert at the Johns Hopkins Proton Therapy Center.

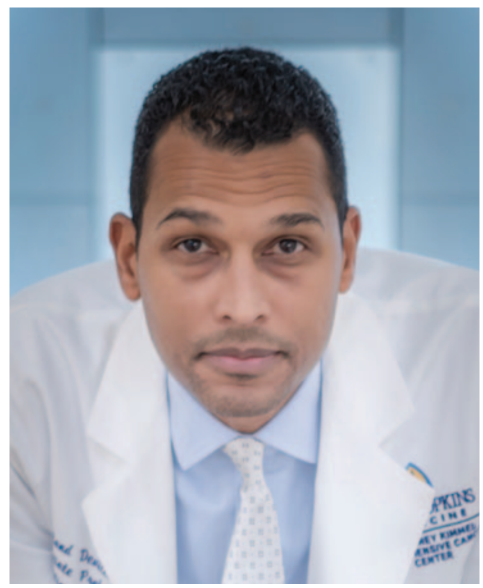
"We will be able to leverage our extraordinary research and clinical talent in order to advance the field," says Viswanathan.

Proton therapy does not replace other forms of radiation therapy. "We do well with all forms of radiation therapy, including stereotactic and brachytherapy treatments, and that's something most other proton centers do



COLLABORATION

Clockwise, top left: **Akila Viswanathan**, M.D., M.P.H., Director of Radiation Oncology and Molecular Radiation Sciences; **Matthew Ladra**, M.D., M.P.H., Director of Pediatric Radiation Oncology; **Christina Tsien**, M.D., Proton Therapy Brain Tumor Specialist; **Curtiland Deville**, M.D., Proton Therapy Center Medical Director; **Jean Wright**, M.D., Director of Breast Cancer Program, Dept. of Radiation Oncology and Molecular Radiation Sciences; **Jeffrey Meyer,** M.D., gastrointestinal cancer expert; **Brandi Page**, M.D., head/neck cancer expert; **Russell Hales**, M.D., Director, Thoracic Oncology Program.



not offer. That's important because not every patient will need proton therapy," says Viswanathan. "Patient care, whatever is the best option for the patient, will guide our decision-making."

The Kimmel Cancer Center's excellence in all areas of radiation therapy makes it possible to offer comparative planning. This means the ability to determine which one of its many radiation treatment tools — proton, photon, CT- and MRI-guided brachytherapy, stereotactic ablative radiation, CyberKnife or brachytherapy — is the best option for each patient.

SOME CANCERS, SUCH AS THOSE IN THE BRAIN OR NEAR VITAL ORGANS, SHOULD GET PROTON THERAPY.

"The kind of radiation our experts perform is very focused in conforming to the tumors," says Viswanathan. "The benefit of an expert team that can make the important comparisons and correctly determine, patient by patient, which form of radiation therapy is the optimal choice cannot be overstated."

Some cancers, such as those in the brain or near vital organs, should get proton therapy, Viswanathan explains. "Some patients might benefit from a combination of types of radiation or chemoradiation. Recent data indicates signficantly less side effects with proton therapy for patients receiving concurrent chemotherapy."

Working with our radiation oncologists, our medical physicists use very fast computers to iterate the plans hundreds of times to arrive at the most ideal way to deliver radiation to each patient. The selected plan is reviewed, modifications are made and it is tested with a virtual avatar of the patient to be sure it has the outcomes anticipated. The end product is precision radiation therapy that has been detailed and confirmed at many levels and specific to the needs of each patient.

The Place for Research

Most experts agree that the ability of proton therapy to spare healthy cells, by zeroing directly on and stopping at the end of tumors, makes proton therapy the radiation treatment of choice for pediatric patients and adult patients with tumors in the brain or on or near the spinal cord, but definitive research studies are essential to advances. One room in the proton center will be dedicated to the cellular, physics and animal studies needed to refine and define who is best treated with proton therapy.

Clinical Director and Proton Therapy Center Medical Director **Curtiland Deville,** M.D., says it is the reason he came to Johns Hopkins. "I wanted to be in an academic center to be at the forefront of solving issues and questions about proton therapy: What are the best indications for proton? Where can we increase benefit, and where can we reduce toxicity? Where are we not getting such benefit and can let go? This is an area that is lacking, and our center can begin to get to the answers." The Proton Therapy Center will be solving these unknowns and leading future progress, says Deville.

Radiation oncologist and gastrointestinal cancer expert **Jeffrey Meyer,** M.D., was drawn to Johns Hopkins for the same reason. Meyer completed a fellowship in proton therapy and says that the Johns Hopkins Proton Therapy Center is one of the few centers addressing complications associated with proton therapy, such as movement of organs and sensitivity to density in organs. All of these questions and concerns can be mitigated with research, he says.

"There are always going to be new technologies. Expertise and the willingness to do research to know how to use it is critical," Meyer says. "It's a great technology we want to take advantage of, but we have to be smart about how we use it."

The Johns Hopkins Proton Therapy Center

What Sets Us Apart

Unparalleled Expertise: Since opening as one of the first comprehensive cancer centers in the nation, Johns Hopkins Kimmel Cancer Center experts have led cancer research, deciphering the causes of cancer and advancing care for the most complex cancer cases. This level of expertise continues with our Proton Therapy Center, which will be directed by the leading radiation oncology and medical physics experts in the world.

Largest and Most Advanced: Our 80,000-square-foot facility is one of the largest and most advanced facilities in the world, with four treatment gantries and dedicated research-specific space.

Imaging Couch and Respiratory Gating: It is the only proton center with CT imaging integrated with treatment to ensure the most accurate and precise treatment planning and delivery of proton beam therapy. Respiratory gating technology tracks the proton beam to movement of the tumor and stops the beam if the tumor moves. Our experts helped invent and develop these technologies.

Pencil Beam and Other Advanced Technologies: It has the latest pencil beam delivery that virtually paints tumors with cancer cell-killing radiation while sparing surrounding normal tissue.

Research Center: As an academic proton therapy center, research will be performed in a dedicated gantry using specialized Johns Hopkins expertise in physics and radiobiology.

Precision Medicine: Our experts take a unique, multidisciplinary and precision medicine approach that brings together all specialists and experts to work with patients to develop individualized, detailed treatment plans specifically suited to each patient.

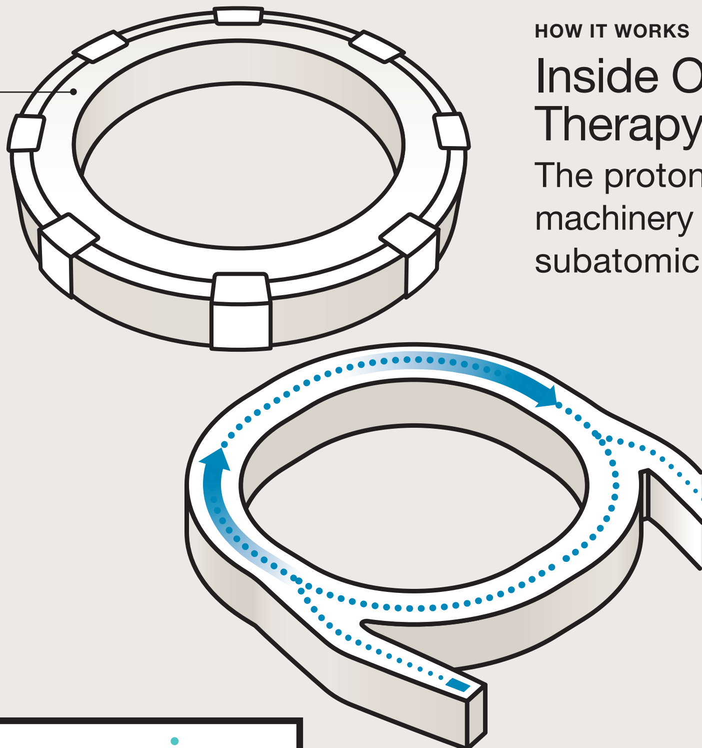
Local, National and International: The Johns Hopkins Proton Therapy Center brings the most advanced cancer care to patients living in the region while also providing care to patients across the U.S. and around the world.

Access for All: Collaboration between the Johns Hopkins Kimmel Cancer Center and Children's National ensures advanced cancer care to patients of all ages, including children and young adults.

HOW IT WORKS

Inside Our Proton Therapy Center

The proton is small, but it takes big machinery to generate and move these subatomic particles for treatment.



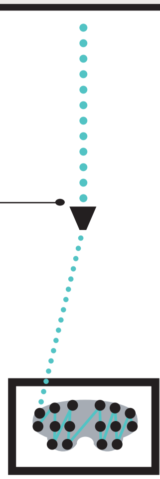
The Synchrotron
A synchrotron is a type of particle accelerator used to accelerate protons for use in proton therapy. It is 26 feet in diameter and composed of a ring of small magnets. Protons are injected into the ring and begin traveling around the ring at great speeds, about 10 million times per second. Put another way, the speed of the protons is so fast, it could circle around the earth five times in one second. It is advanced technology over earlier generations of proton therapy because it can produce beams of a wide range of energies and reduces the risk of unnecessary and unwanted radiation to the patient.

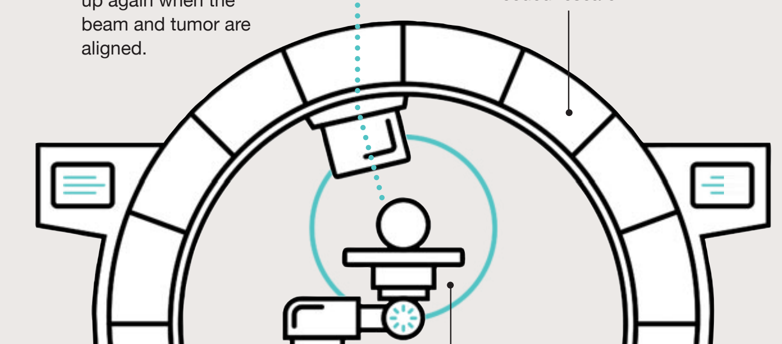
Gantries
Protons travel down magnetic devices into the treatment rooms. A 360-degree, rotating, 30-foot-diameter iron framework, called a gantry, controls the speed and direction of protons. It allows radiation oncologists to direct the beam at any angle and deliver the proton beam with pinpoint accuracy to a patient's cancer.

Our center has four of these, three rotation for adult and pediatric treatment, and one fixed beam for much-needed research.

Respiratory Gating
The slightest motion can cause tumors to move. Our proton therapy beam tracks directly to the tumor, stopping if the tumor shifts with the patient's breathing and starting up again when the beam and tumor are aligned.

Pencil Beam Scanning
This new technology funnels the protons into a narrow beam—just a pencil tip's width—coming out of the proton therapy machine hundreds of times per second, scanning the tumor back and forth and up and down, just to the edges of the tumor, to paint it layer by layer with the cancer-killing proton beam. Our advanced technology is intensity modulated, making it possible to deliver varying degrees of energy targeted to the specific composition of each area of the tumor.





On-Board Imaging
Ours will be among the first to have on-board imaging. Plans for a CT Couch, invented by medical physics Director **John Wong** in collaboration with Hitachi, will provide a built-in CT scanner that merges images of the cancer taken during treatment planning with ones taken the day of treatment to verify that the tumor being treated has not changed or moved. It facilitates precision treatment within one-tenth of 1 millimeter accuracy.

Q & A

WHAT IS PROTON THERAPY?
Proton therapy is an effective way of killing cancer while minimizing harm to healthy, surrounding tissue. What sets proton therapy apart is that it literally "paints" cancerous tumors, layer by layer, killing the cells with a high-energy pencil beam. Our highly trained team of physicians and physicists directs the proton beam to the desired site with pinpoint accuracy, and treatment is conformed to the size and shape of the tumor. The proton beam releases its energy entering the tumor and stops at the tumor. There is no exit dose, so the risk of harm to healthy surrounding tissues is reduced. As a result, proton therapy may lower treatment side effects and improve patient outcomes.

WHAT CANCERS DOES PROTON THERAPY TREAT?
Because of its precision, proton therapy is preferred for adult and pediatric patients with brain and spinal tumors. In children, cancers can be treated without harming developing brains and growing bone. Since the proton beam conforms to the tumor and does not have an exit dose, it minimizes radiation going to normal cells, which can result in the development of second cancers later in life. This is particularly important for pediatric and young adult patients. Proton therapy may also be useful for certain patients with sarcoma, breast, prostate, lung, head and neck, liver, and pancreatic tumors. The proton beam, with its precision accuracy, is also favored when tumors are resting near the heart or major arteries and blood vessels.

IS PROTON THERAPY RIGHT FOR YOU?
At Johns Hopkins, unique multidisciplinary clinics evaluate each patient to determine if proton therapy is the right treatment. They offer patients a comprehensive consultation with the entire team of experts, including our proton therapy experts. Our physicians and nurses work with patients to develop an individualized, detailed treatment plan specifically suited to each case.

WHY DOES EXPERTISE MATTER?
Technology is only as good as the experts who use it. The Johns Hopkins Kimmel Cancer Center and the Department of Radiation Oncology and Molecular Radiation Sciences have a long and proven history of leading cancer research and advancing cancer care. This expertise sets the Johns Hopkins Proton Therapy Center apart.

Advanced Technologies

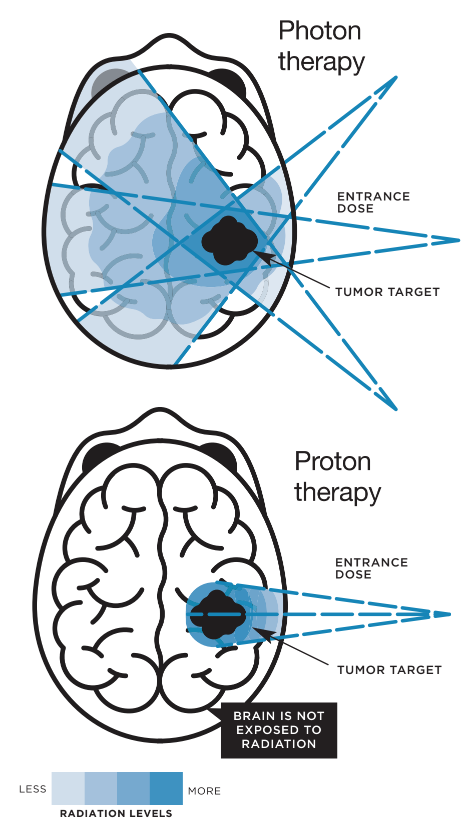
Even before the research begins, Viswanathan is confident that the Johns Hopkins Proton Therapy Center is poised to deliver unprecedented care. Our 80,000-square-foot proton therapy center is the largest in the country and has four rooms, including three with gantries — the large, sphere-shaped structures that house the equipment used to deliver proton therapy to patients. The gantry rotates around the patient, delivering the proton beam at any angle necessary to target the cancer.

Unique features, including the pencil beam, a tumor-tracking system that allows the beam to adjust to tumor movement, in-room imaging via a CT couch and the Oncospace data registry are unique to the Kimmel Cancer Center, and make the proton therapy we provide the safest and most advanced available.

Our Proton Therapy Center is outfitted with the most up-to-date pencil beam technology, which only recently became available. The pencil beam paints tumors with cancer cell-killing energy layer by layer, staying within the boundaries of cancer. The technology is so advanced that it is able to modulate intensity, delivering varying degrees of energy based on the specific makeup of the tumor, adjusting to differences throughout a tumor to provide the right amount of energy to every area.

Collaboration among Kimmel Cancer Center molecular radiation scientists and the manufacturer of our proton therapy system means our Proton Therapy Center will usher in more advanced tumor monitoring that makes the already safe and targeted pencil beam patient-specific and even more tumor-specific. One method uses molecular monitoring to evaluate the tumor and adapt radiation treatment to each patient. Molecular imaging allows doctors to differentiate cancer

As protons travel through the body, most of the energy is reserved and released where the protons stop in the tumor. Photons, on the other hand, release energy along the entire path they travel. This fundamental difference is what makes proton therapy preferential for certain tumors in the spinal cord and the brain. If vital organs or structures are along the path the radiation travels, protons cause less damage to them. And there is no exit dose.



cells from scar tissue or other ambiguous lesions and better define the anatomy of the tumor and its response to radiation treatment.

Another advanced technology, called respiratory gating, tracks motion in the lung and stops the beam if the beam and tumor lose alignment due to motion caused when patients breathe. The beam works when it is lined up with the tumor and stops when it is not lined up. The Johns Hopkins Proton Therapy Center will be conducting research on the use of gating in treatment planning.

The Proton Therapy Center also has magnetic resonance, or MR, and CT imaging, as well as a new type of CT scan called dual energy CT, which provides detailed information on the specific makeup of the area around the tumor. This advanced and unmatched imaging makes our proton therapy the most precise of any available today.

Proton for Pediatrics

One area where most experts agree the benefit has clearly been demonstrated is in pediatric patients.

Matthew Ladra, M.D., M.P.H., director of pediatric radiation oncology at Sibley Memorial Hospital, earned a proton therapy-specific fellowship mainly focused on pediatrics.

"When children get exposed to radiation at a young age, they are at much higher risk for issues down the road when they are long-term survivors," says Ladra. "Our goal is to radiate what's supposed to be radiated and leave everything else alone. Proton therapy helps us do that."

"When children get exposed to radiation at a young age, they are at much higher risk for issues down the road when they are long-term survivors. Our goal is to radiate what's supposed to be radiated and leave everything else alone. *Proton therapy helps us do that.*"

MATTHEW LADRA

THIS PHOTO WAS TAKEN BEFORE THE COVID-19 PANDEMIC.

INNOVATION
(Left) **Heng Li,** Ph.D., Chief Proton Physicist,
(Right) **John Wong**, Ph.D., Director of Medical Physics

"WE ARE BRINGING WORLD-CLASS CANCER CARE AND CUTTING-EDGE RESEARCH TO PATIENTS HERE AND AROUND THE WORLD."

A unique partnership with Children's National Hospital that began in 2016 creates one of the largest pediatric radiation oncology programs in the country. The patient volume and clinical collaborations, including joint clinical trials and research initiatives with the National Institutes of Health, are expected to speed clinical discovery.

Watch "We Speak Proton":
http://bit.ly/2COSKAM

NEWS & UPDATES

TARGETED THERAPIES
IMMUNE THERAPIES
ADVANCED TECHNOLOGIES
ONGOING RESEARCH
CANCER TREATMENTS

AKILA VISWANATHAN NAMED DIRECTOR OF RADIATION ONCOLOGY AND MOLECULAR RADIATION SERVICES

AN ORGAN-SPARING OPTION FOR GYNECOLOGIC CANCERS

In July 2020 **Akila Viswanathan**, M.D., M.P.H., was named Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

While serving as Director of Radiation Oncology for the National Capital Region, Dr. Viswanathan led the October 2019 opening of the Johns Hopkins Proton Therapy Center, one of the largest and most advanced centers in the U.S.

As a leader in the field of radiation oncology, she has developed numerous clinical innovations, published more than 200 articles and chapters and lectures nationally and internationally.

Viswanathan was the first in the U.S. to use real-time magnetic resonance-guided interstitial brachytherapy for the treatment of gynecologic cancers. After establishing a program at the main Johns Hopkins Kimmel Cancer Center location in East Baltimore, she brought the therapy to its Sibley Memorial Hospital location.

Using active magnetic resonance imaging (MRI) guidance, physicians insert several hollow catheters into the tumor. Radioactive seeds about the size of a grain of rice tethered together by a long thread are inserted into the catheters and remain there for about 10 minutes, providing a rapid but high dose of radiation to cancer cells. A computer controls the insertion and removal of the seeds, ensuring a precise dose throughout the tumor.

"Gynecologic cancers can grow fast and require a very focused high dose to attack the tumor," Viswanathan explains.

The entire outpatient procedure takes just a few hours and provides a lifetime of benefit to patients. That was her motivation for developing the procedure.

"I want women who have inoperable cancer that is limited to the gynecologic area to be cured of their cancer," she says. Women who have surgery for cancer often lose their entire gynecologic tract, including the cervix, she explains. Brachytherapy preserves these organs, which is particularly important for young women.

The procedure was first done with CT guidance, but Viswanathan says studies show better cancer control and survival rates with MR guidance, so now she only performs MRI-guided brachytherapy.

"Tumors can be very large and can extend into the bladder and rectum, and MR allows us to see all of the places the tumor is located," she says. The types of MR technology she uses are unique. Working with a team of physicists who write special codes to direct the MR scanner, she can look inside a tumor and provide a variety of details not available with traditional MRI.

Outcomes are excellent for cervical cancer and recurrent uterine, vulvar and vaginal cancers. Viswanathan says published data shows MR-guided brachytherapy survival rates of over 90%. As a result, Viswanathan is in demand, seeing about 300 patients a year from all over the world.

On the research side, she has studied combining drug therapies with brachytherapy, including using drugs that block blood supply to tumors and ones that boost the immune response. She is also collaborating with gene sequencing expert **Srinivasan Yegnasubramanian**, M.D., Ph.D., on a precision medicine approach. By sequencing the genome of tumor samples obtained at biopsy, she can begin to define biomarkers that distinguish otherwise similar-looking cancers. Information like this can help better guide treatment.

NEW FUND HONORS THEODORE DEWEESE BY ADVANCING CANCER RESEARCH

A LEAD GIFT from Erwin and Stephanie Greenberg established the **Theodore L. DeWeese**, M.D., Award for Innovative Cancer Research in the Department of Radiation Oncology and Molecular Radiation Sciences. The fund honors DeWeese's commitment to innovative and high-value patient care and expert research, and will advance cancer research by supporting projects across departments and specialties.

An annual award of up to $100,000 will be presented to one or more individuals committed to innovative research in radiation oncology and the radiation sciences, with the goal of better serving patients. The Greenbergs asked DeWeese to direct the fund, giving him discretion to select recipients from throughout The Johns Hopkins University, including medical students, residents, fellows, physician trainees, physics trainees, research scientists and faculty members, who are undertaking novel and inventive approaches in cancer research and the treatment of cancer.

The inaugural recipients of the award are **Ana Kiess**, M.D., Ph.D., and **Amol Narang**, M.D. (See pages 13 and 14 for more information on their research.)

"Ted is a remarkable physician, mentor and human being, and he was instrumental in the creation of the Department of Radiation Oncology and Molecular Radiation Sciences. His heart is in radiation oncology, where he has established a culture of excellence in patient care and discovery. Our hope is that many others will join us and the fund will grow, providing new opportunities for investigators to emulate Ted's commitment and advance the field in his honor. It gives all of us an opportunity to participate in the discovery process," say Erwin and Stephanie Greenberg.

DeWeese, who oversaw radiation oncology gaining departmental status in 2003, served as director of the department until 2018, when he was named vice dean for clinical affairs.

"I am incredibly appreciative and humbled by this honor," says DeWeese. "Obtaining funding for novel ideas is difficult, particularly for our young investigators. This award will allow rapid pursuit of ideas and concepts that, if proven, can be leveraged into larger, competitive grants."

From left: Amol Narang, M.D., Stephanie and Erwin Greenberg, Theodore DeWeese, M.D., Ana Kiess, M.D., Ph.D., Akila Viswanathan, M.D., M.P.H.

THIS PHOTO WAS TAKEN BEFORE THE COVID-19 PANDEMIC.

Spacer Shields Nearby Organs in Pancreatic Cancer Treatment

JOHNS HOPKINS researchers are testing whether a biodegradable hydrogel with the consistency of toothpaste could help protect the duodenum (the head of the small intestine) during radiation therapy for pancreatic cancer.

If successful, the spacer could help solve a problem in pancreatic cancer, for which advanced radiation therapies are increasingly used to target locally advanced cancer that cannot be surgically removed. These therapies work best when clinicians can increase the radiation dose over time, but there is a limit to how much radiation can be used before "spilling over" to harm healthy tissue.

DING

"It's important to deliver a high amount of radiation to the tumor to achieve a good outcome," says **Kai Ding**, Ph.D., assistant professor of radiation oncology and molecular radiation sciences, "but for the pancreas, it's difficult because the duodenum, the stomach and the liver are all close to the pancreas. We can still deliver radiation, but it's not the level of radiation that we want."

The hydrogel separates the two organs by about 8 millimeters. "This extra space allows the radiation to fall off so that the duodenum receives a much smaller dose," he says.

A multi-institution clinical trial for patients with locally advanced pancreatic cancer and patients with borderline resectable pancreatic cancer — pancreatic tumors that have attached to nearby blood vessels, making surgical removal of the entire tumor difficult or even impossible — has started to further study the biodegradable spacer gel, which he says disappears from the body in about six months.

Hydrogel spacers are most commonly used in the treatment of prostate cancer, but Ding says they are being studied in liver cancer, treatment for which also has the potential to affect nearby organs in the crowded abdomen, in gynecologic cancers in the pelvis, and head and neck cancers to shield saliva-producing glands.

To develop a new type of therapy called **NANOPARTICLE HYPERTHERMIA**, radiation oncology researcher **Robert Ivkov**, Ph.D., is collaborating with a multi-institutional and multispecialty team of researchers, including Johns Hopkins veterinarians **Dara Kraitchman,** V.M.D., Ph.D., and **Rebecca Krimins**, D.V.M; radiation oncologist **Lawrence Kleinberg**, M.D.; medical physicist **Kai Ding**, Ph.D.; and radiation therapists and Mount Sinai neurosurgeons **Costas Hadjipanayis,** M.D.; and **Alexandros Bouras**, M.D.

TURNING UP THE HEAT ON TUMORS

Robert Ivkov

Robert Ivkov, Ph.D., wants to enlist iron oxide nanoparticles, each about a million times smaller than a human cell, as tiny but potent weapons in the treatment of tumors. Injected as part of a saline or water solution directly into tumor tissue, the nanoparticles can be heated using oscillating magnetic fields produced by a device developed in Ivkov's lab. The heat stresses the tumor cells and should make them more vulnerable to other cancer therapies, he says.

"By heating the tumor this way, we could actually make a dose of radiation or chemotherapy more effective," says Ivkov.

Nanoparticle hyperthermia is unlikely to be a stand-alone treatment, Ivkov says, but paired with other therapies, it could address an unmet treatment need for some inoperable brain and pancreatic cancers.

"This is a potential tool that gives clinicians and their patients some measure of improvement in controlling that large or advanced local tumor," he notes. "Or it could help in managing side effects by allowing the clinician to treat the tumor with a lower dose to help reduce the issues with toxicity, or with the same doses to make the radiation much more effective."

For more than five years, Ivkov has been working with colleagues at the Johns Hopkins Kimmel Cancer Center and the Icahn School of Medicine at Mount Sinai to refine and test the nanoparticle heating technique on mouse models of glioblastoma to determine how heated nanoparticles could act as a radiation-enhancing agent. He and his collaborators applied for National Cancer Institute funding to study the treatment in glioblastoma in veterinary dog patients. They hope to begin treating canine patients within the next two years at the Johns Hopkins Center for Image-Guided Animal Therapy and in the Department of Radiation Oncology and Molecular Radiation Sciences with a novel combination of surgery, nanoparticle hyperthermia and chemoradiation.

"We want to study all aspects of nanoparticle hyperthermia with radiation in a spontaneous disease model that more closely resembles human disease, and in particular, we will be asking, is this combination curative, will it reduce tumor size, will it reduce tumor recurrence, what are the side effects and toxicity?" says Ivkov. "The results from mouse models have shown significant promise to treat glioblastoma, but mouse models can only get us part of the way," adds Ivkov. By treating dog patients, the research team hopes to develop techniques to improve treatments for both human and animal patients suffering from deadly brain tumors.

INJECTED AS PART OF A SALINE OR WATER SOLUTION DIRECTLY INTO TUMOR TISSUE, HEATED NANOPARTICLES CAN STRESS TUMOR CELLS AND MAKE THEM MORE VULNERABLE TO OTHER CANCER THERAPIES.

One particular challenge with direct delivery of nanoparticles is tracking where nanoparticles go when they are injected. Imaging the nanoparticles in tissues has proved beneficial from previous work conducted by Ivkov and his radiology colleagues. They discovered that the nanoparticle solution doesn't spread uniformly through the disorganized tissue of a tumor, which can lead to difficulties for treatment.

This uneven distribution means that when it's time to heat the nanoparticles, there are inevitable "hot" and "cool" spots in the tumor. The researchers are experimenting with ways to heat the particles quickly and then reduce the temperature to allow the heat to dissipate through the tumor. Adjusting the heat output of the nanoparticles is accomplished remotely by simply adjusting the power of the magnetic field device at the control panel. Ivkov claims this is a key advantage of magnetic hyperthermia. When combined with an image of the nanoparticle distribution in the tissues, Ivkov and his team are confident that mathematical models of tissue heating and heat transfer can provide the needed guidance to adjust magnetic field controls to manage the heat therapy. "We need to reliably achieve a minimum dose in as large a volume of the tumor as possible without overheating normal tissues, and that's the challenge," Ivkov explains. Ivkov and his team integrate materials science, physics and engineering with medicine to develop new approaches for difficult diseases such as glioblastoma.

The nanoparticles also can be delivered intravenously, tagged with small molecules or antibodies that change the way in which the nanoparticles interact with the body's immune system. This systemic use of nanoparticles is more suited to metastatic cancer, the researchers say. Already, Ivkov and others observed that nanoparticles delivered in this way can stimulate the body's immune system, triggering an anti-cancer immune response. **Preethi Korangath**, a member of Ivkov's research team, has recently discovered that antibody-labeled nanoparticles are preferred by immune cells residing in cancer tumors. This finding offers new potential to attack other cells that support the growth of the cancer cells.

This discovery was made with initial research funding provided by the Jayne Koskinas Ted Giovanis Foundation for Health and Policy (JKTG Foundation). A new round of funding from the JKTG Foundation enabled Ivkov, Lombardi Comprehensive Cancer Center breast cancer researcher Robert Clarke, Ph.D., and Johns Hopkins veterinary pathologist **Kathleen Gabrielson**, D.V.M., Ph.D., study this immune response in more detail to understand how it could be strengthened or prolonged and what features of the nanoparticles are responsible for inducing these effects. "The nanoparticles are about the same size as pathogens like viruses, and it's possible that our immune systems have evolved to pay attention to foreign bodies that are in a specific size range," Ivkov says.

INNOVATION

Molecular radiation sciences researchers discover a new vulnerability in cancer cells.

MOLECULAR RADIATION SCIENCES researchers discovered a new vulnerability in cancer cells that provides an opportunity to develop new cancer drugs. **Marikki Laiho**, M.D., Ph.D., the Willard and Lillian Hackerman Professor of Radiation Oncology and director of molecular radiation sciences, discovered new drug-like molecules that effectively killed cancer cells. Researchers found that the molecules specifically blocked RNA polymerase 1 (Pol 1) and that cancer cells rely on a Pol 1 pathway much more than normal cells. This discovery led to a new opportunity for a targeted therapy that disrupts cancer cells with little harm to healthy ones. The drug could also augment the benefits of radiation therapy.

Cells have three main ways — Pol 1, 2 and 3 — to read the instruction manual that is our DNA and convert those instructions into protein-based actions that are dictated by genes. Pol 2 is studied most in cancer because it executes the primary program that orchestrates the expression of defective proteins related to the majority of cancer mutations identified to date. The other two polymerases, however, provide essential molecular tools that help make the actual proteins. “Pol 1 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 Pol 1 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.”

This research was propelled by funding from foundations supporting cancer research, the National Institutes of Health, and recently, Bluefield Innovations, a collaboration between healthcare investment management firm Deerfield Management and The Johns Hopkins University.

“The challenge is to cross the ‘Valley of Death,’ to move the lab discoveries to the clinic,” says Laiho. “The process is costly and complex. It needs a team of experts, and I truly appreciate the opportunity to align with collaborators that share the same mindset and goals to push early-stage research targets forward,” says Laiho. She says her team, medicinal chemist James Barrow at the Lieber Institute, and Kimmel Cancer Center researchers provide expertise and support and have conducted the extensive work required to develop the Pol 1 inhibitors into an investigational new drug. This is a critical step in overcoming a common barrier to advancing promising investigator-initiated drug discoveries and to initiating the first clinical trials.

“Dr. Laiho’s promising research may prove to be a transformational cancer treatment. We’re excited about this progress and new opportunity,” says **Akila Viswanathan**, M.D., M.P.H., Director of Radiation Oncology and Molecular Radiation Sciences.

Discovery Leads to New Clinical Trial for Prostate Cancer

ANDROGEN SUPPRESSION is a widely used tool in the fight against prostate cancer. Prostate cancer cells are stimulated by male hormones called androgens, such as testosterone, and suppressing or blocking androgens can starve cancers of these hormones and help kill them.

However, when cells that have been starved of androgens are later exposed to them again, it triggers a cascade of events. One of these is the reorganization of the DNA, says radiation oncologist and prostate cancer expert **Daniel Song**, M.D., who is collaborating with **Srinivasan Yegnasubramanian**, M.D., Ph.D., and **Theodore DeWeese**, M.D., to turn this cancer vulnerability into a new treatment.

SONG

DEWEESE

YEGNASUBRAMANIAN

As the DNA is reorganized, it is cut in many places, Song explains. These breaks, known as double-strand breaks because they go through the double helix that characterizes DNA, are often too difficult for cells to repair, and so the cells die. Building upon research in mouse models by radiation oncologist and prostate cancer expert DeWeese and prostate cancer and molecular biology expert Yegnasubramanian, Song is conducting a clinical study funded by The Patrick C. Walsh Prostate Cancer Research Fund that uses the double-strand breaks to augment radiation therapy.

"The androgen receptor triggers DNA enzyme activity, including an enzyme called topoisomerase 2-beta, which cuts DNA. We believe giving radiation therapy on top may kill prostate cancer cells better than radiation alone or androgen receptor agonist stimulant therapies alone," says Song.

Prostate cancer cells are stimulated by male hormones called androgens, such as testosterone, and suppressing or blocking androgens can starve cancers of these hormones and help kill them.

The radiation treatment comes in the form of brachytherapy, a procedure in which radioactive seeds are injected into prostate tumors to kill cancer cells.

Song explains that patients will be on androgen suppression therapy for one month leading up to brachytherapy. The night before brachytherapy, patients will take a single dose of the drug flutamide, which is FDA-approved for prostate cancer but also has a paradoxical effect of partially stimulating the androgen receptor. Laboratory studies have shown that giving flutamide with radiation is more effective at killing prostate cancer cells compared with either one alone. Giving flutamide before treatment in patients who are on androgen suppression therapy may make brachytherapy work even better.

"Cancer cells already deprived of androgen that then get restimulated with flutamide respond with more DNA breaks," Song explains.

A 24-patient clinical trial is planned to confirm that the DNA breaks observed in animal studies also occur in patients receiving flutamide.

Radiation Therapy Can Help Make Cancers Operable

Amol Narang, M.D., is focused on advanced technologies and discoveries that allow for the delivery of higher and more precise doses of radiation to pancreatic cancers, with the aim to improve survival.

One approach allows surgeons to successfully remove more cancers that were previously thought to be inoperable, which is necessary for patients to have a chance to get well.

Building upon research using a very precise, high-dose form of radiation therapy known as stereotactic ablative radiotherapy, Narang can get high doses of radiation to pancreatic tumors that have attached to nearby blood vessels, a situation that makes surgical removal of the entire tumor difficult or even impossible. These cancers are referred to as borderline resectable (operable) or locally advanced cancers.

"There are a number of key blood vessels that course near the pancreas, and as pancreatic cancers abut, encase or occlude these vessels, it becomes harder and harder for surgeons to successfully remove cancers without leaving cancer cells behind," explains Narang. Surgeons must peel the cancer away from these delicate vessels, adding to the complexity of the already complicated surgery and increasing the chances that a few cancer cells will be left behind, which can later result in the cancer recurring or spreading.

Stereotactic ablative radiotherapy is focused radiation that reduces exposures to surrounding tissue and organs, and makes it possible to deliver higher doses of radiation to tumors over a relatively short period of time: five days versus six weeks with conventional radiation therapy. Combining modern combination chemotherapy and stereotactic ablative radiotherapy in patients with pancreatic cancers that have attached to blood vessels can help tumors shrink away from these vessels, making surgery possible for more patients.

"Surgery offers patients the only chance for a cure, and patients who undergo successful surgeries live longer on average as compared with those who can't have their tumors removed," says Narang. "Patients with locally advanced and borderline resectable cancers who undergo successful removal of their tumors experience survival that is similar to patients who don't have blood vessel involvement and go straight to surgery."

There is also evidence that high doses of radiotherapy may make cancer cells more responsive to subsequent treatment with immunotherapy. Radiation damage to the tumor may make it more recognizable to the immune system and may prime patients to respond better to new drugs that give the immune system an upper hand on cancer. The potential of this immune-boosting component in pancreatic cancer is currently the focus of clinical trials.

"New technologies are allowing us to safely get higher doses of radiation to pancreatic tumors, providing more patients with an opportunity for a surgical cure."

Narang says improvements in endoscopic procedures are allowing radiation oncologists to deliver radioactive treatment internally to pancreatic tumors. Using endoscopy-guided ultrasound to direct the placement of this treatment, Narang can inject radioactive material directly into the pancreas tumor, which may allow an increased radiation dose to be directly delivered to the tumor without harming other tissues and organs.

"New technologies are allowing us to safely get higher doses of radiation to pancreatic tumors, providing more patients with an opportunity for a surgical cure," says Narang.

RADIATION TREATMENT DURING THE PANDEMIC

A message from Dr. Akila Viswanathan, Director of Radiation Oncology and Molecular Radiation Sciences

THE SAFETY OF our cancer patients throughout the pandemic has been and continues to be our top priority. We work closely with our colleagues in epidemiology and infection control to implement safety practices.

Our radiation oncology faculty, nurses and staff received extensive COVID-19 preparation and training. When possible, virtual telemedicine appointments are offered to patients. For patients who must come to us in person for treatment or other care, we implemented rigorous COVID-19 precautions at our front doors and in our waiting rooms and clinical treatment areas.

Every patient receives a COVID test, so that we can attend to patients who may need to pause treatment as they recover from a COVID infection. Patients who are experiencing symptoms or have been admitted to the hospital receive a COVID test.

We established biocontained simulation and treatment rooms for adult and pediatric patients at our East Baltimore campus. These rooms are uniquely set up with special air flow and filtering to care for patients with infectious diseases, keeping them safe and cared for while preventing the spread of the infection to other patients. During this time of pandemic, we are providing service and aid to patients throughout our Maryland and Washington, D.C. communities, caring for many patients transferred from other hospitals and clinics that do not have the infection control capabilities to care for COVID-positive patients.

I am pleased to report that our safety precautions and frequent COVID testing have kept our patients and dedicated healthcare staff safe.

WEB EXCLUSIVE: Listen to *On Target* with Dr. Akila Viswanathan who delves into cutting-edge science with her team of radiation oncologists. https://**hopkinskimmel.libsyn.com/category/Dr+Akila+Viswanathan**

KIESS

Radiation Therapy in Drug Form

A TEAM of radiation oncologists, radiochemists and biologists are collaborating to develop radiolabeled drugs as a new way of delivering cancer cell-killing radiation to prostate cancer cells. Radiation therapy comes in many different forms, explains radiation oncologist **Ana Kiess**, M.D., Ph.D.,who is spearheading studies with **Martin Pomper**, M.D., Ph.D., an expert in transforming imaging agents into therapeutic agents.

Although many are familiar with radiation therapy that uses beams to deposit energy that kills the cancer cells, radiopharmaceuticals are radiation therapy in medicine form. Kiess and Pomper are adapting a radiolabeled agent that is given at very small doses for diagnostic imaging PET scans for therapy.

The agent is used in imaging to make cancer cells visible, but when used at a higher dose and targeted directly to cancer cells, it can also kill the cancer. Kiess and Pomper use prostate-specific membrane antigen (PSMA) as the delivery method for the radiolabeled drug. When the drug is injected via IV, it automatically travels to PSMA-expressing cells.

“PSMA is present in the normal prostate, present in the brain, the kidney, salivary glands and the intestines, but it’s expressed much higher in prostate cancer cells,” Kiess says. Her first focus was to make sure they could deliver the drug to cancer cells without harming normal cells. The drug will go into any cell that expresses PSMA. Prostate cancer cells express 100 times more PSMA than kidney and salivary cells, and as an added protection, Kiess and collaborators worked with chemists to modify the drug and make it more specific to tumor cells and less likely to go into normal cells.

The drug, called LU-PSMA-R2, will soon be studied in a multicenter international clinical trial in patients with advanced prostate cancer. Findings from Kiess’ laboratory research that served as the foundation for the clinical trials were published in the *Journal of Nuclear Medicine* in 2017 and won the Editor’s Choice Award.

PSMA is also present in kidney cancer, glioblastoma brain cancer, pancreatic cancer, and some head and neck cancers, opening the door for the drug to be used for other cancers if the prostate cancer trials are successful.

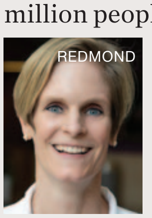
Corey's Story

OVERCOMING A SPINAL TUMOR

COREY LIDONNE

WHEN 32-YEAR-OLD Corey LiDonne isn't busy at his job at Facebook, the electrical engineer-turned-construction manager can often be found outdoors in Oregon skiing, hiking along the coast or camping on the beach while taking in the surrounding bluffs and cliffs, a backdrop of which he never tires. But recently, Corey had to interrupt his busy lifestyle to confront a surprising diagnosis.

In February 2019, he was diagnosed with sacral chordoma, an aggressive but slow-growing form of cancer so rare it's detected only in about one in 1 million people per year and just 300 patients in the United States annually. Corey wasted no time gaining access to the best treatment he could find. From his home on the West Coast, he researched his options. Within a week, he contacted Johns Hopkins and got on a plane headed to the Kimmel Cancer Center for a consultation with neurosurgeon **Sheng-Fu Larry Lo**, M.D., radiation oncologist **Kristin Redmond**, M.D., and other experts in the Spinal Tumor Multidisciplinary Program.



REDMOND

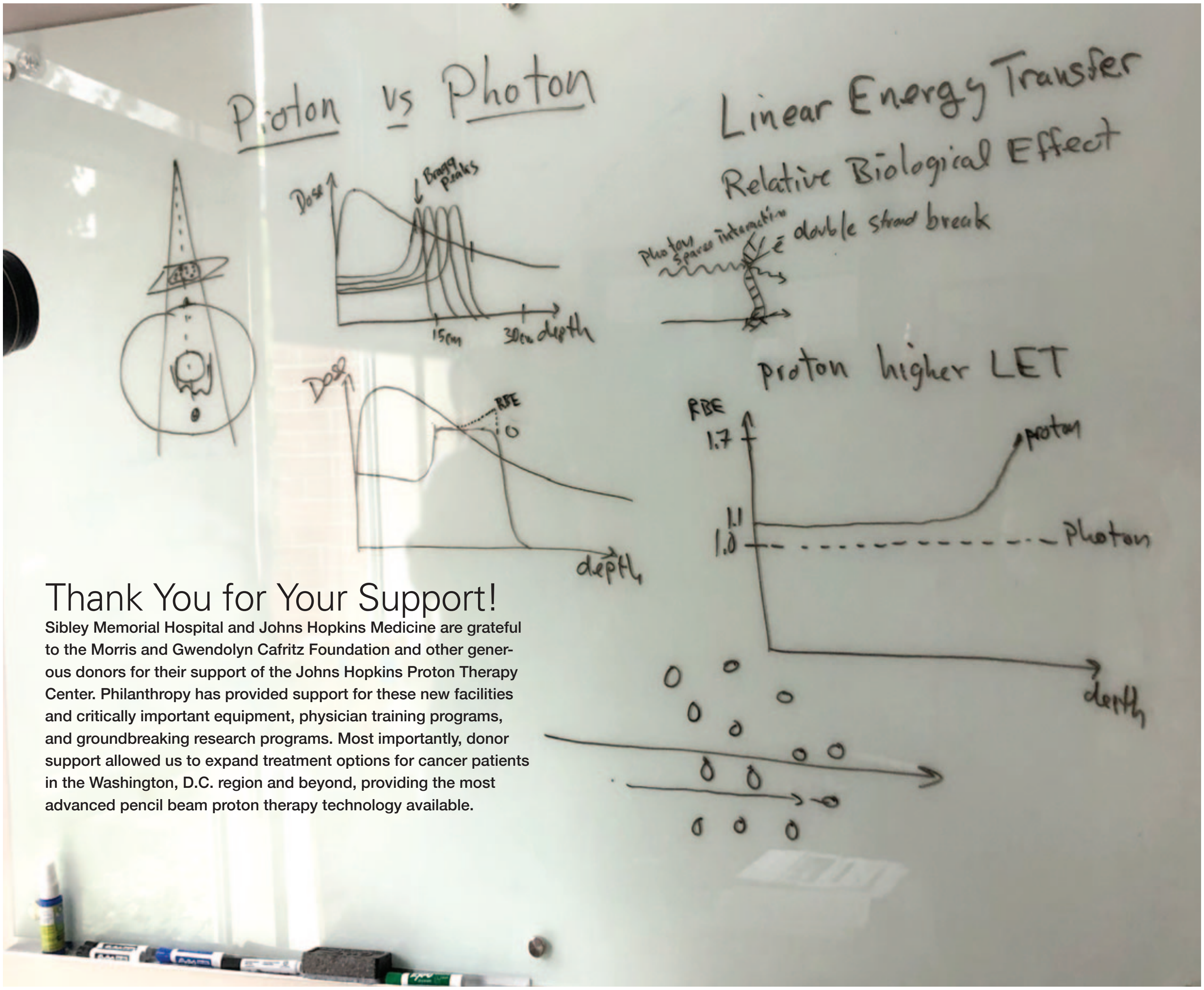
Corey says the easy accessibility to members of Johns Hopkins' treatment team reaffirmed his decision to head east. The multispecialty team of experts explained images of Corey's MRI and CT scans to show him exactly where the tumor was and discuss their plan to remove it.

Despite the rare nature of chordoma, the Kimmel Cancer Center treats a relatively large number of patients with this type of cancer, says Redmond, who leads the spine radiosurgery program. This larger caseload gives Redmond and the team opportunities to use therapies that other hospitals may not have the experience to employ. Redmond says she uses stereotactic ablative radiation therapy, for instance.

"Stereotactic radiation gives a high dose of radiation to the tumor, keeping areas around it at low dose. So far, we've had excellent outcomes with minimal side effects," says Redmond.

About a month after his diagnosis, Corey underwent stereotactic radiation: five 90-minute sessions on consecutive days. He says he experienced only slight grogginess and nausea during treatment. About a month after the radiation, he had surgery at Johns Hopkins to remove the tumor.

As his life has taken this unforeseeable turn, Corey finds reassurance in the stability of his medical team. "Johns Hopkins is comprehensive. Drs. Redmond and Lo collaborate on a daily basis. All the doctors I need are right there," says Corey, who has his sights set on returning to his active lifestyle in Oregon.



Thank You for Your Support!

Sibley Memorial Hospital and Johns Hopkins Medicine are grateful to the Morris and Gwendolyn Cafritz Foundation and other generous donors for their support of the Johns Hopkins Proton Therapy Center. Philanthropy has provided support for these new facilities and critically important equipment, physician training programs, and groundbreaking research programs. Most importantly, donor support allowed us to expand treatment options for cancer patients in the Washington, D.C. region and beyond, providing the most advanced pencil beam proton therapy technology available.

Help Us Make a Difference

Each contribution to the Johns Hopkins Kimmel Cancer Center makes a difference in the lives of cancer patients here at Johns Hopkins and around the world.

Our physician-scientists are leading the way on many of the scientific breakthroughs in cancer, and your donation will support patient care and innovative research that is translated to better, more effective treatments. We are also focusing on ways to prevent cancer and support survivors.

You may designate a gift to a specific faculty member.

To make your donation online

hopkinscancer.org and click *"Make A Gift"*

To mail your donation

Johns Hopkins Kimmel Cancer Center
750 E. Pratt St., Suite 1700
Baltimore, MD 21202

To contact our Development Office

Phone: 410-361-6391
Fax: 410-230-4262
Email: KimmelGiving@jhmi.edu

Visit us on the Web

hopkinscancer.org.

JOHNS HOPKINS
MEDICINE

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER