A Spectrum of Achievements
A Decade at the Department of Radiation Oncology and Molecular Radiation Sciences

FALL/WINTER 2014
Radiation Oncology and Molecular Radiation Sciences
Past, Present and Promise

RADIATION ONCOLOGY HAS come a long way since its origins as an offshoot of the department of radiology and later as a program of the department of oncology. Although, we only recently celebrated the 10th year as our own department, our history of excellence in cancer research and patient care and the integral role it has played in the management of cancer are not new.

What started more than four decades ago as a program built around the cancer-fighting power of targeted X-ray beams has evolved significantly. These healing rays are still essential to the care we provide, but we have grown into so much more. Molecular radiation sciences, knifeless radiosurgery, proton beams, radiosensitizers, nanoparticles, radiolabeled drugs, targeted and immune-stimulating therapies, informatics systems, efficiencies models, and inventions that propel research and make the clinic safer are now part of our 21st century science and medicine.

We have built upon the strengths and the work of early pioneers to create a program of radiation oncology and molecular radiation sciences that is second to none. Our experts have earned recognition as world leaders in developing transformational concepts and translating basic developments into novel therapies that have changed the standard of care and improved the lives of patients with cancer. You will read about many of the advances in this special issue of Promise & Progress.

The ingenuity of our clinicians and scientists and the progress we have made in the last ten years has exceeded my expectations, and it points to the boundless possibilities before us. I marvel at the talent we have amassed here. Our physicians, scientists, physicists, nurses, technologists, residents and students, and administrative staff have collectively and collaboratively pointed us toward the future.

Of course, none of our success would be possible without the support of the many gracious donors who provided a fertile foundation for novel ideas to flourish. The growth in science, talent, and equipment that allows us to meet increasing patient demands and to continuously innovate safer and more effective treatments is made possible through their generous commitment.

I am honored and humbled to lead a department so steeped in talent and promise. As we mark this milestone and reflect on our rich history, the unprecedented progress of the last decade, and the breakthroughs on the horizon, the future looks bright. I can only imagine what the next ten years will bring.

Theodore DeWeese, M.D.
Director and Kimmel Professor of Radiation Oncology and Molecular Radiation Sciences
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
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How We are Harnessing it to Fight Cancer

Undeterred. This may be the best word to describe the tenacity of Kimmel Cancer Center radiation oncology clinicians and scientists in advancing patient care and radiation science. When others were content with the status quo, they resolved to do better than the best. This persistence sparked inventions, innovations and adaptations that have benefitted patients and expanded the scope of radiation science. This setting where engineering gadgets, feats of physics, and medical science collide, is the ultimate laboratory. If it can be imagined, they are determined to achieve it.
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.

Wharam began his career at the same time that deaths from cancer were rising, and then-President Richard Nixon announced a national war against cancer. Sites for National Cancer Institute-funded comprehensive cancer centers were being determined, and Johns Hopkins was selected to be home to one of the first. It was then that 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 bear testimony to his pioneering contribution to advancing the care of children with cancer. 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.

In 1975, just 50 percent of children diagnosed with cancer survived. 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 research which 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. It was not good enough for him. He talks of a young girl he treated for Hodgkin’s lymphoma. She 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.

This was not something Wharam took lightly. “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. He was a leader in the early research that led to scaled back treatment for many diseases. “I had two missions,” 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, 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’s 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.

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. 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 zeroes in on tumors and 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 on the Kimmel Cancer Center’s Washington, D.C., campus and is scheduled for completion in 2018, 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 new collaboration with Children’s National Medical Center. Under the direction of pediatric radiation oncologist Stephanie Terezakis, the Kimmel Cancer Center will become the exclusive provider of radiation 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.

He points to photographs in his office and smiles. “This little girl just graduated from college. This one is married now and has a baby. See this one—I treated her for brain metastases, and she survived,” says Wharam. His face lights up when he speaks of his patients. It is clear that they are his fondest memories from a long and impressive career.

He has retired from seeing patients now and has turned the reins over to Terezakis. 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 and people like Stephanie Terezakis are 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.”

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—MOODY WHARAM
A DECADE OF DISCOVERY

2003 • The Department of Radiation Oncology and Molecular Radiations Sciences 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 • Physician-scientist Phuoc Tran 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, Dr. Tran showed that high-dose statins reduce c-myc activity.

2013 • Marikki Laiho uncovered a potential way to stop cancer cells in their tracks. The research focuses on the RNA polymerase pathway, POL I, 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, Ted DeWeese 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.

READ MORE ABOUT THE HISTORY OF RADIATION ONCOLOGY AT JOHNS HOPKINS AT HOPKINS CANCER.ORG.
The Inventor

John Wong sees problems and he fixes them. A physicist rather than a physician, he does not treat patients. Instead, his mind is always working on ways to help patients by putting better tools in the hands of physicians. He is focused on logical ways to make equipment work better, which allows researchers to dig deeper and move faster so they can get improved treatments to patients.

“We recognize that in radiation oncology, we need the right balance of technology development, laboratory research, and dissemination of knowledge for clinical decisions,” says Wong.

He is the quintessential scientist, the one with endless ideas and a multitude of projects. Many are able to identify the problems, but few can envision and create the remedies as Wong does. He smiles, and his voice is filled with excitement as he talks about his inventions. It is not an overstatement to say they have revolutionized the field of radiation oncology.

Some inventions, like the active breathing coordinator (ABC) provide somewhat simple fixes to significant problems. The ABC is a non-invasive, interactive device that coordinates breathing with radiation treatment. As patients breathe, tumors move, and ABC locks the breath in place for short, comfortable periods to ensure the tumor is not a moving target, making sure the radiation hits the cancer.

Another, cone-beam computed tomography (CBCT), has become an integral part of radiation oncology treatment and research. CT imaging delivers clear images of bone, soft tissue, and tumor, making it a desirable guidance system for radiation treatment. The cone beam, which uses a cone of divergent X-rays, captures images of the patient on the treatment machine to allow quick and more accurate irradiation of the tumor.

The invention referred to as SARRP, for small animal radiation research platform, is a favorite and staple among radiation oncology scientists, because it transforms radiation research done with animal models. “Before SARRP, there was no laboratory counterpart for what we do in the clinic,” says Wong. That was unacceptable, so he invented a downsized version of a human machine for mice. With unprecedented precision, investigators can use Wong’s machine to perform human-quality radiation delivery on mice. It provides a realistic model to study what they do in treatment. “In radiation oncology, we don’t have the means to study mechanisms in a living animal subject, and this machine helps us do that,” says Wong.

In radiation oncology there is nearly equal interest in how to destroy tumors as there is in how to prevent damage to normal tissue. Being able to study human therapies in animal models is paramount to developing more effective and safer ways to treat patients. A recent improvement he made to SARRP addresses another critical need. “One of the biggest problems we have in radiation oncology is not the treatment technology but rather the ability to characterize the

“We recognize that in radiation oncology, we need the right balance of technology development, laboratory research, and dissemination of knowledge for clinical decisions.” —John Wong
The work of Laiho and team is focused on understanding the mechanisms cancer cells use to sense and repair DNA damage and to maintain their own survival. “This has tremendous relevance in radiation oncology, because we don’t want cancer cells to be able to make repairs after treatment,” says Laiho. She and her team are looking for kinks in cancer cells’ armor that they can exploit to prevent them from making these fixes. “If we can give a drug that blocks DNA repair and follow it up with radiation treatment, maybe we can kill more cancer cells,” explains Laiho. They have made significant progress toward this goal.

Raven has been licensed to an outside company and is currently in testing. Wong has already moved on to his next project—Raven II, which will incorporate quality assurance measurements for personalized treatment of individual patients.

The Scientist
When radiation oncology received departmental status in 2003, the establishment of a research arm, molecular radiation sciences, was a priority for Ted DeWeese. He selected basic scientist Marikki Laiho to head the research program.

“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 Laiho, the Willard and Lillian Hackerman Professor of Radiation Oncology. “Now, we combine technology with biology, and that ultimately means improved treatments for patients.”

The device is named Raven, in honor of Baltimore’s beloved football team. Wong competed for the Alliance BioMaryland LIFE Prize to develop his product the week after the Ravens won the 2013 Super Bowl. The alliance competition is judged by pharmaceutical and biotech executives, medical device designers and manufacturers, entrepreneurs, venture capitalists, and angel investors with the goal of helping Johns Hopkins faculty commercialize their research and technological innovations. It is science and medicine’s version of Shark Tank, the reality TV show in which inventors try to get backing for their products. Wong won the Life Prize competition.

He competed against scientists who were pitching exciting new drugs, but they had at least to years of validation work ahead of them before their products could be commercialized. Wong’s invention was a quality assurance device that connects to linear accelerators—the high-tech machines that produce the beams of radiation during treatment—and performs a series of measurements to verify that the machine is functioning correctly. It could be ready for market in less than a year, and it would be appealing to any clinic providing radiation therapy.

The Raven device performs measurements in a fraction of the six to eight hours each month per machine it would typically take a physicist. The measurements are essential to patient safety and quality delivery of care, because they ensure the machines are generating and delivering radiation accurately. Currently, the device operates as a standalone system for a clinic, but companies that manufacture linear accelerators envision incorporating it as part of the quality assurance accessories that accompany new machines. It is expected to be particularly useful in developing nations with less skilled manpower to perform the timely measurements manually.

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She credits the young investigators she has recruited with the success. “DNA damage biology research is not unique, but our focus is,” says Laiho. “There is not a radiation and molecular sciences re-

THE WORK OF MARRIKI LAIHO AND TEAM IS FOCUSED ON UNDERSTANDING THE MECHANISMS CANCER CELLS USE TO SENSE AND REPAIR DNA DAMAGE AND TO MAINTAIN THEIR OWN SURVIVAL. SHE AND HER TEAM ARE LOOKING FOR KINKS IN CANCER CELLS’ “ARMOR” THAT THEY CAN EXPLOIT TO PREVENT THEM FROM MAKING THESE FIXES.
Discoveries in Molecular Radiation Sciences

DNA Damage Report

**PARP Inhibitors**

Young investigator and pediatric oncologist **Sonia Franco** is exploring cell repair molecules known as PARP (Poly ADP ribose polymerase) proteins. She has found that using drugs called PARP inhibitors to shut down this repair function in cancer cells increases the killing power of radiation treatment. Franco, who is fascinated by the complexity of the PARP-deficient mouse model, has uncovered a previously unrecognized complexity to PARP-like proteins—a family of 17 different proteins. She is working to decipher their functions and their potential role in cancer therapeutics. She has built new mouse models to conduct experiments aimed at solving these mysteries. Her unique insight led the American Association for Cancer Research to designate one of her recent research publications as a “must-read.”

Radiation oncologist and breast cancer expert **Richard Zellars** and colleagues are studying PARP inhibitors and pre-operative radiation in patients who have received chemotherapy as their first line of treatment but still have cancer remaining. In this Breast Cancer Research Foundation-funded study, women with advanced, treatment resistant cancers are given three weeks of radiation and treatment with an oral PARP inhibitor. PARP inhibitors sensitize cancers to radiation. “These women have the worst prognosis and very few treatment options. Their cancers tend to advance quickly, but we are seeing large tumors shrink to just a few scattered cells,” says Zellars. “We are the first to do a study like this, so we are proceeding slowly and cautiously, but the early results are looking very promising. We are getting great responses in the worst cases of breast cancer. If we can get these results in the most advanced cases, we should really be able to get even better responses in patients with earlier stages of cancer.”

**DNA Damage Signaling**

**Mihoko Kai** is focused on understanding cell signaling pathways for DNA damage and, in particular, the role they play in deadly glioblastoma brain cancers. Kai wants to understand the relationship between two natural processes—DNA repair and cell cycle checkpoints—and how it contributes to cancer cell development and survival. While each has been well studied individually, Kai is among the first to explore how they work together in cancer.

**DNA Damage Checkpoints in Cancer Therapies**

**Fred Bunz** is researching why some tumors respond well to radiation and cancer chemotherapies and others do not. He is working to learn if they have constitutive differences that dictate their responses to therapies and if they are dependent on the DNA damage responses. Identifying those differences could be extremely important in selecting the optimal treatments for each patient. Bunz is using genetic tools that he has created to selectively introduce cancer-specific mutations into tumor cells so that he can explore and observe how they respond to cancer therapies. His research has revealed a rich and complex landscape of alterations that dramatically changes how the tumors respond to treatments.

**RNA Particles**

Department director **Ted DeWeese** is working to identify new radiosensitizing agents. The goal is to combine radiation with factors that render cancers— but not normal tissues—vulnerable to DNA damage. Working in collaboration with Department of Urology basic scientist **Shawn Lupold**, they have shown that blocking DNA repair does just that and devised a strategy to deplete the cells of repair factors by using RNA-mediated silencing of the repair genes. Moreover, they used RNA particles, called aptamers, to deliver the silencing RNAs specifically into the cancer cells. This approach has been highly successful in killing prostate cancers and tumors in mouse models and will soon be ready for clinical trials.

**Robert Ivkov** is a physical chemist whose research is focused on magnetic nanoparticles and their uses to improve the effectiveness of radiation therapy and imaging. He has developed particles that generate intense heat when they are exposed to alternating magnetic fields and improve magnetic resonance and x-ray CT imaging. Heat is an excellent agent that increases the sensitivity of cancer cells to radiation. He has developed novel nanoparticles, and also builds the instruments that generate the alternating magnetic fields. Tests have now been conducted in models of several types of cancer—including prostate, breast, liver and pancreas—with impressive improvement of tumor control when the nanoparticle heating is combined with low doses of radiation. Enhancing the effectiveness of radiation therapy with heat offers potential to treat patients with lower radiation doses and minimize severe side effects.
In her own research, Laiho has made an exciting discovery that appears to stop cancer cells in their tracks. The studies are in an early stage, but they have demonstrated the ability in laboratory and animal studies to completely shut down the cellular machinery cancers need to survive.

The research focuses on the RNA polymerase pathway, called POL I, 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. “Without this transcription machinery, cancer cells cannot recover,” says Dr. Laiho. “The cancer cells cannot function.”

POL I is known as a transcription pathway. It is how proteins, which direct cell division, are translated and put into action by cells. Uncontrolled cell division is a hallmark of cancer, and BMH-21 has demonstrated an ability to bind to the DNA of cancer cells and completely shut down this transcription pathway, stopping cancer cells’ ability to replicate.

Preliminary studies were completed using human tumor cells obtained through the NCI-60 platform, a collection of 60 human tumor cell lines of nine different cancer types. Laiho and team collaborated with experts from the National Cancer Institute’s Developmental Therapeutics Program who tested their molecule for potential anticancer activity. BMH-21 showed 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.

With these promising results, Laiho has been busy working to move her findings to clinical trials. She turned to drug discovery expert James Barrow from the Lieber Institute for Brain Development, located at the Science + Technology Park at Johns Hopkins. Barrow analyzed 30 new synthesized molecules based on BMH-21. Analysis of these results confirmed the predicted mechanism of action. “This tells us that our thoughts that BMH-21 works by binding to DNA was spot on,” says Laiho. “The fact that the activity of the original molecule is very confined suggests that we’re near the optimal stage.”

Laiho says this is a somewhat unusual occurrence in drug discovery. Typically, many revisions to the lead molecule are required before it is ready for clinical studies. “We are very excited, because it means we are closer to the clinic than we could have ever imagined would be possible,” says Laiho.

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. The Prostate Cancer Foundation is helping Laiho get there, awarding her a $1 million Global Treatment Sciences Challenge Award. The funding will allow her to test BMH-21 or one of its derivatives in animal models of advanced prostate cancer. Collaborating with Kimmel Cancer Center prostate cancer experts Angelo De Marzo, Vasan Yegnasubramanian, bioinformatics specialist Sarah Wheeler, and University of Maryland, Baltimore County animal tumor model scientist Charles Bieberich, Laiho hopes to interest pharmaceutical companies by demonstrating the drug’s effectiveness against cancers where treatment options are scarce, such as prostate cancer that has spread beyond the prostate.

That said, the exquisite beauty of Laiho’s discovery lies in its application across many cancer types. “It appears to work in any solid tumor with high dependency on the pathway,” says Laiho. “The transcription machinery the compound shuts down is common among all cancer cell types, so even though we are looking at prostate cancer, we believe it has broad therapeutic potential.”

In a personalized cancer medicine approach, De Marzo has developed biomarker tests that would identify prostate cancers that highly express the pathway and would be likely to respond to the drug. Similar approaches could be used in other cancers. “The more a tumor depends on this pathway, the better this treatment should work,” says Laiho.

Studies have demonstrated the ability in laboratory and animal studies to completely shut down the cellular machinery cancers need to survive.
Better Models of Care

It is not always a sophisticated new device or clever invention that propels science and medicine forward. Sometimes monumental advances are the result of ingenuity and imaginative perspective—a different way of using the data or technology we already have or a better way of structuring or delivering care.

Big Data: The Next Medical Frontier

The era of 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 challenge is figuring out what information has the value to advance patient care and how to extract it.

“There is 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 it 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 setting. “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 this data in completely new ways.”

Beginning with astronomy professor Alexander Szalay, who developed a computerized system to survey large swaths of the night sky and to store, measure and analyze properties of 300 million galaxies, Johns Hopkins University scientists have been out front pioneering technologies that analyze data sets too large for the human mind to manage unassisted. Johns Hopkins University president Ronald Daniels recognized what could be accomplished in science, medicine, and public health with the ability to decode the immense amount of data collected every day at the university and made big data analysis an institutional priority.

The success of individualized medicine—the ability, among other things, to determine which patients will benefit from a particular drug or treatment and which ones will not—rested on the ability to conquer big data. In the Kimmel Cancer Center, McNutt’s work was one of the first practical demonstrations of this promise. “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.

Radiation oncology is a data intensive treatment, and DeWeese believed his department provided fertile ground for such an innovative, data-driven project. As did Scott Zeger, a Bloomberg School of Public Health biostatistician and proponent of individualized health who was following McNutt’s work with Oncospace and was one of its biggest fans. Oncospace was another example of Johns Hopkins’ leadership in informatics, and Zeger worked with President Daniels, McNutt, DeWeese, radiation oncology physicist John Wong, and computer science professor Russ Taylor to secure early funding for it from the Commonwealth Foundation, Maritz Foundation, Philips Corporation, and Elekta Corporation. More recently, they earned a grant from information technology giant Toshiba to incorporate imaging into the data collected.

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 provided the critical link. He could put the system McNutt designed to the test in clinical practice. This was the moment McNutt had staked his career on. It was what drove him from the corporate setting, where he was designing radiation treatment planning systems, to the Kimmel Cancer Center. “I could tell you very accurately where the radiation dose goes,” says
McNutt. “The important question in treating patients is where should it go and where shouldn’t it go?” That was the central question that Oncospace could answer, but unlike McNutt’s other inventions, this one could only be tested in the clinical setting through direct collaboration with physicians.

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, but they do not want to be left unable to speak or eat—some of the toxic effects radiation treatment of head and neck cancers can cause.

It was the reason McNutt saw these cancers as the ideal choices to put Oncospace to the test. Head and neck cancers are among the most difficult cancers for radiation physicists and oncologists to plan, 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 could provide the guidance that would allow 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. 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.

“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.” He was sold, but head and neck cancer treatment involved more than one specialty, and he recognized that getting the entire team of clinical specialties on board was paramount to achieving the full value Oncospace could offer.

As important then 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 required 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.”

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.

This is where the Toshiba grant is playing a major role, joining Phillips and Elekta in providing funding and scientific expertise to help McNutt and team adapt the Oncospace system to incorporate data 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 tempera-
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, he 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, then more data analyzed should lead to more rapid discovery of better roadmaps for care. Partner institutions would be given access to Oncospace technology and would share their results with all of the others participating centers. McNutt says sharing the technology with other institutions will also allow many cancer types to be studied simultaneously.

The success of individualized medicine—the ability, among other things, to determine which patients will benefit from a particular drug or treatment and which ones will not—rested on the ability to conquer big data.
This was the concept of radiation oncologist Joseph Herman. He was a member of the pancreatic cancer clinical team who was faced with growing numbers of patients from across the country seeking appointments because of a promising vaccine therapy developed by Kimmel Cancer Center scientists.

“The fight against cancer is not only a biological one,” says Herman. “It also requires getting patients involved in treatment decisions and making care convenient, safe, and affordable for patients, and this is where I felt like we could improve.”

Herman overcame many challenges in getting the clinic off the ground, not the least of which was the reluctance of the other Johns Hopkins specialists involved in treating pancreatic cancer patients. It wasn’t that they thought Herman’s idea was bad; they simply wondered if it was feasible to get all of the experts—more than a dozen people—together in one room, one day each week, to review cases and decide on a course of treatment.

He persevered, and the pancreatic cancer Multi-D clinic became a reality. The clinic revolutionized and optimized how pancreatic cancer patients were cared for at the Kimmel Cancer Center. In fact, it became the model for how all cancer types are managed in the Cancer Center.

Still, Herman thought it could be even better. “The care we were providing was great, but we were limited by the number of patients we could see,” he says. The opportunity to remedy this problem came from a talented and forward-thinking young resident, an M.D./M.B.A., who was coming to train in the Department of Radiation Oncology and Molecular Radiation Sciences.

The resident, Shereef Elnahal, had developed an operations management system that he wanted to test out in the pancreatic cancer Multi-D clinic. Elnahal is among a growing class of physicians coalescing the practice of quality medicine and the business of quality medicine.

Historically, physicians focused on providing medical care and left the business decisions to administrators. In today’s climate of physician shortages, rising healthcare costs, and large managed healthcare systems, more and more physicians, like Elnahal, are pairing their medical degrees with business degrees and taking an active role in problem-solving. With serious issues making news headlines, like the mishandling of patients at Veterans Administration hospitals across the U.S., managed healthcare—or what could more aptly be described as mismanaged healthcare—had captured the public’s attention. Elnahal believed he had the solution, and the Kimmel Cancer Center was the ideal place to test it.

A dual M.D./M.B.A. graduate from Harvard, Elnahal was already an accomplished doctor, and had published research on this topic while still a medical student. He would likely have been a top residency choice for any of the country’s best medical institutions. Ted DeWeese, the Department of Radiation Oncology and Molecular Radiation Sciences Director, says Elnahal was one of the finest candidates he had ever interviewed, so he was thrilled that Johns Hopkins was his first choice.

Elnahal was drawn to Johns Hopkins because of Peter Pronovost’s internationally recognized patient safety models and Herman’s pioneering efforts to establish the pancreatic cancer Multi-D clinic. In his dual medicine/business studies, Elnahal had first planned to major in health policy, but was frustrated with the lengthy time lag between ideas and actually effecting a policy change. Instead, he chose to focus on business efficiency models. “At the organizational level, one can pilot change and influence people to change behaviors, and they can obtain effects in a very short time,” says Elnahal. “If a model works, you can scale it up throughout hospital systems and influence policy on a national level.”

Elnahal believed the Kimmel Cancer Center was the perfect testing ground for his medical adaptation of a business model. His goal was to improve the efficiency of its cancer clinics, starting with the pancreatic cancer Multi-D clinic. Almost every other industry had proven
that efficiency models could result in near-perfect quality, says Elnahal. He points to the airline industry as an example. “Planes don’t crash very often, and that’s because the airline industry knows how to organize operations to prevent mistakes,” he says. He felt strongly that the same philosophy could be applied to medicine with similar results.

With DeWese and Herman on board, Elnahal put his plan into action. Within a year, the pancreatic cancer Multi-D clinic was seeing results. Before Elnahal’s model was put into place, the pancreatic cancer clinic could accommodate four to five patients per week. With Elnahal’s model in place, 12 to 15 patients were being seen in the clinic each week.

How did he do it? Elnahal says he applied an amalgamation of two business models, lean methodology and the Military Acuity Model, to healthcare. These models are used in the corporate world to prioritize tasks, drilling down to a core set of essential actions that, if missed, would result in a compromised product, safety, or function. In the pancreatic cancer clinic, Elnahal worked with the clinical team to pare down a task list of 20 to 30 actions that were routinely performed for each patient to just six that they determined were essential to quality patient care. If one of these six tasks were missed, it could predict clinic delays and potentially compromised care. “We found that many of the things that had become standard practice in the clinic—things people thought had to be done—were duplicative or not as relevant to clinical outcomes as they thought,” says Elnahal.

Essential tasks included having patients’ scans and diagnostic test results available to physicians on the clinic day or sooner, gaining a general understanding of patients’ presumed disease stage, assessing pain and other health problems that could impact the treatment plan, and evaluating social risk factors that could derail treatment.

The key to the system’s success is care coordinators, says Elnahal. The clinic coordinators are knowledgeable about patient care and the flow of the clinic, and those things that tend to interrupt flow. Often “those things” are missing scans or insurance issues.

“A patient thinks they have received preauthorization for a CT scan. They get to Johns Hopkins and find out they are unable to get the CT,” explains May Hodgin, the pancreatic cancer clinical care coordinator. In the past, residents and fellows might be scrambling to solve the imaging problems, and the patient’s appointment would be delayed, often disrupting other patient appointments for the remainder of the clinic. In Elnahal’s model, Hodgin works with administrative support staff member Lindsay Parish to ensure everything needed for the appointment is in hand before the patient arrives. If there is an additional test or scan required, they handle the insurance preauthorization and bring the patient in the day before so all of the information the clinic team needs to make treatment decisions is there for their review before they meet with the patient.

“We are learning everything we can about the patient before they walk in our door,” says Herman. “In the past, we would schedule people in clinic, look at their records, and then figure out what they need. It makes much more sense to properly triage people in advance, and that’s what Dr. Elnahal’s system does so well.”

The past habits often left clinical staff working frantically to get tests scheduled or to locate additional records. “It is in these types of situations that caregivers are most likely to become overwhelmed,” Elnahal says, “and that is when things get missed.” Elnahal’s model frees up doctors and nurses to make clinical decisions and safely reallocates other tasks to administrative staff members. “This model absolutely works,” says Hodgin. “We are a well-oiled machine now. We rock and roll.” She says the patients like it because they have a constant point of contact and their appointments run smoothly. When clinics run smoothly, the physicians and nurses also like it better.

The system is structured to fluidly assess workloads to prevent any person from becoming overloaded with assignments. If that is in danger, the clinical care coordinator is triggered to redistribute tasks. As a result, all members of the team report feeling less burdened. In fact, administrative staff members express a higher job satisfaction because they are now directly engaged in the clinical mission of the Kimmel Cancer Center. Doctors report feeling less stressed; even though they are seeing more patients, they are less bogged down with administrative tasks and able to focus fully on what they were trained to do—practice medicine.

Much like personalized cancer medicine gets the right treatments to the right patients at the right time, Elnahal’s system gets the right task assigned to the right person at the right time. “The model allows us to make excellent use of the faculty and staff we have,” says Elnahal. “If we had to hire more people, it wouldn’t be economically feasible, but the value of this is that it improves efficiency, quality of care, and employee satisfaction using the talent we already have.”

To convince the skeptics who question whether efficiency necessarily equates with quality care, Elnahal reviewed key indicators, such as increased phone calls from patients following appointments with questions and a rise in emergency department visits. After his model was implemented, there was a significant decrease in patient phone calls and a slight decrease in emergency visits, despite a greater volume of patients being seen. While not a scientific survey, he says it is evidence nonetheless that the model is providing the value they were after.
“The fight against cancer is not only a biological one. It also requires getting patients involved in treatment decisions and making care convenient, safe, and affordable.” — JOSEPH HERMAN

"The care we were providing was great, but we were limited by the number of patients we could see," says Joe Herman (left). The opportunity to remedy this problem came from a talented and forward-thinking young resident Sherief El Nahal (right).
“We’re getting at least the same quality of care, and probably slightly better,” says Elnahal. Moreover, the model has increased patient volumes while lowering costs because more patients are being cared for with the same level of resources.

With these promising results, Elnahal and team are now working to tailor the business model more specifically to cancer care and deploying it throughout the radiation oncology department. He has added more individualized care coordination specific to each phase of cancer management, including diagnosis, treatment, and survivorship as well as a coordinator to guide patients as they navigate each of these phases.

“Cancer is not like other diseases,” says Elnahal. “We recognized that there are several distinct phases and that many patients may transition between phases more than once; patients in the survivorship phase, may experience a recurrence and find themselves back in the diagnostic and treatment phase. Distinct care coordination for each phase and each transition improves the efficiency and quality of care.”

Lauren Rosati, a research assistant and clinical care coordinator on the path to medical school, is working with Elnahal to secure continued funding for the efficiency project, helping ensure that the success of the pancreatic cancer Multi-D can be put to use in other multi-D clinics. Rosati experienced the pancreatic cancer Multi-D when a close family member began treatment. “At the end of the day, the patient and family is our main priority,” says Rosati. “We must focus on what is best for them and how we can make their cancer diagnosis and treatment most bearable for everyone involved. Most often, the factor most likely to improve overall patient experience is care coordination and communication—and this is what our model targets.”

Elnahal is also working with Kimmel Cancer Center chief administrative officer Terry Langbaum to extend use of the method to all of the center’s outpatient clinics. The Veteran’s Administration has also expressed interest in using the model to improve its outpatient care.

“One of the problems in medicine is that we tend to do things the same as practitioners before us have done them. We don’t stop to think about ways to do it better,” says Herman. “Shereef has caused us to look at things in a new way,” he says. “Now we are the trail blazers, excited to expand this model throughout Hopkins and beyond.”

The Harriet and Jerry Dempsey Scholars for Cancer Research Fund

A $1 million gift from Harriet and Jerry Dempsey has provided much-needed support to clinician-scientists-in-training in the Department of Radiation Oncology and Molecular Radiation Sciences. The research fund provides promising young investigators and clinicians, like Shereef Elnahal and Andrew Sharabi, the opportunity to work side by side with established experts while pursuing their own areas of interest. “We have been fortunate to attract the best of the best. Our residents are involved in pioneering, high-impact research,” says Theodore DeWeese, M.D., Director of the department. “The generous gift of Mr. and Mrs. Dempsey to support these fabulously talented young trainees reveals the Dempsey’s passion for excellence and our shared vision for improved care of cancer patients, now and in the future.”

See “The Resident's Model, page 13” and “Focused Radiation Stimulates Cancer Immunity,” page 26, to read more about the impressive projects of current residents Shereef Elnahal and Andrew Sharabi.

Fixing the Target

Breathing is something we don’t give much thought to unless we have a disease or injury that impairs it or unless we deliberately choose to hold our breath. Otherwise, it is another exquisite process of the human body that is controlled by our brain without any conscious effort required by us.

This paradigm shifts when it comes to radiation treatment of lung cancer. Breathing makes tumors a moving target. With every inhale and exhale, the tumor moves. If the radiation beam is not adjusted to this movement, it misses the cancer and hits normal tissue. As a result, radiation physicists and oncologists use a few techniques and technologies to incorporate movement into treatment planning, but radiation oncologist and lung cancer expert Russell Hales says there have been no studies that compare the technologies head to head to determine the best way to predict tumor movement.

With the explosion of new technologies, each with unique strengths and weaknesses, the key is to match the tool to the job.

One technology, developed by Kimmel Cancer Center physicist John Wong, takes advantage of our ability to consciously control breathing—to safely hold our breath for brief periods. Active breathing control (ABC) technology is based upon this but incorporates additional guidance and controls. The patient has a plastic tube in his or her mouth and is given instructions off and on throughout treatment to take a deep breath and hold it. ABC locks the breath in position so that the patient’s tumor does not move. The technology works well to stabilize tumor movement and has become a staple in radiation therapy.

The negative outcome is that it increases the time it takes to treat patients. Patients are treated in 20-second intervals. ABC assists them in holding their breath for a
It is a reasonable approach, but it may not be realistic, Hales says, because it does not take into account spontaneous irregularities that occur in normal breathing, such as sighs, yawns, and coughs. He says 4-D MRI, which uses a magnetic field and radio waves instead of X-rays to capture images, can be safely used to capture longer periods of breathing—as much as 30 minutes—and may offer a more accurate picture of breathing-related tumor movement. Plus, it provides the clearest image of tumors. “When you get a 4-D MRI of the chest, you see nothing but the tumor,” says Hales. “It doesn’t do a good job of imaging the lungs, but it provides a beautiful picture of how the tumor moves.”

Then there is the increasingly popular Cyberknife, robotic radiosurgery. It has become a desirable option for early lung cancers, particularly in the community setting, because of its low toxicity and rapid recovery times. This technology incorporates infrared sensors, much like the motion detectors used in interactive gaming systems, positioned on the patient to track chest wall movement. This process assumes that tumor movement tracks with chest wall movement, but Hales says the movement of the chest wall as a proxy for tumor movement has not been fully validated.

Hales currently has a project funded by the National Institutes of Health to study 4D MRI as a way of confirming or refuting the accuracy of image-based projections of tumor movement. Hales says the problem is that no one has done studies to prove if any of these technologies accurately capture tumor movement or if one technology is better than another. “They may or may not be. We can’t be sure because no one has done the comparisons,” says Hales.

Yet it is critically important to make these determinations because in radiation
“We have to make sure radiation is hitting the tumor and missing critical structures… These things are important, and we are one of the few places in the world doing this kind of research.” —RUSSELL HALES

treatment, precision is paramount. “We have to make sure radiation is hitting the tumor and missing critical structures, and that it’s properly adjusted to avoid other risks in the patient’s anatomy—an abdominal aneurysm, for example” he says.

Hales is planning a study that compares each of the technologies and performs the measurements to confirm or refute the accuracy of image-based projections of tumor movement. “These things matter, and we cannot rely on unproven assumptions,” he says. “We are one of the few places that are doing this kind of research.” When completed, Hales says it should reveal—through evidence-based, quantitative science—the best and most accurate measurement of tumor movement.

Tiny Samples are Key to Individualized Treatment

Radiation oncologist and pancreatic cancer expert Joseph Herman has been relentless in his efforts to improve the delivery of care in the pancreatic cancer clinic at the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, but he has been equally relentless about advancing care for patients with the most difficult cancers.

Stereotactic body radiosurgery (SBRT) is an option for patients who have pancreatic tumors that cannot be removed through traditional surgery. This treatment, sometimes referred to as knifeless surgery, provides high but super-focused doses of radiation to destroy tumors while limiting side effects to nearby normal organs and tissue. As a result, it can be delivered in combination with cancer-fighting vaccine therapy and aggressive chemotherapy.

Information about what drugs will work against a cancer is contained within the cancer’s DNA. Cancer’s “answer key”—the mutations and alterations to genes that drive the cancer to grow and spread—is revealed through sequencing of tumor DNA. Drugs that target these alterations can be identified, so sequencing is particularly useful in patients with difficult-to-treat and resistant tumors that stop responding to standard therapies.

“The problem with patients who have unresectable pancreatic cancer is that it can be difficult to get an adequate sample of the tumor for genetic sequencing,” says Herman. Through a collaboration among Herman, surgeons Christopher Wolfgang and Vicente Valero, and pathologist Christine Iacobuzio-Donahue, he realized that the solution was an adaptation of a procedure they were already doing.

Before pancreatic SRRT is performed, tiny gold seeds, about the size of a grain of rice, are inserted by needle into the pancreatic tumor. These seeds, known as fiducials, serve as reference points to guide radiation oncologists as they treat the cancer. When the seeds are being placed in the pancreas, Herman proposed that they use the same needle to also remove tiny pieces of the tumor for genetic sequencing. The procedure is called a fine needle aspiration and is commonly used to biopsy suspicious masses in the pancreas. The samples are studied under the microscope for the presence of abnormal cells.

For the process to work for genetic sequencing, experts would need to go beyond seeing abnormal cells to seeing inside the abnormal cells. Herman was unsure if the small bits of tumor that could be taken out through fine needle aspiration would provide enough material to sequence the cancer. “We were the first ones to try this,” says Herman, “and we proved that it could be done. You can sequence tumors from these tiny samples, and this genetic analysis could ideally be used to individualize treatment in patients with inoperable pancreatic cancer.”

Saving Brains and Ears

Cancer is a disease that knows no boundaries. It can—and does—attack almost any part of the body, and with devastating consequences. Still, there is something unique about cancer that invades the brain. The brain is the control center for human body, and cancer in the brain can quickly claim a life. But more than that, it can steal the very essence of an individual—the ability to love, to speak, to create memories and interact with family members and loved ones.

Radiation oncologist and brain cancer expert Lawrence Kleinberg understands the special complexity of these cancers better than most. One of his specialty areas is treating patients with cancers that have spread to the brain. These cancers are often so advanced that they have also begun to invade other parts of the body. Almost any type of cancer can spread to the brain, but breast, lung, kidney and melanoma are the most common.

Kleinberg knows he cannot cure these patients, but of all of his work, he finds
the treatment of these patients to be the most gratifying. His goal is to preserve the function of the brain for patients so they can live out whatever time they have on their terms—not the cancer’s terms.

Most of Kleinberg’s patients continue to work and participate in their regular activities. The tool he uses to achieve these results is targeted radiosurgery. The treatment allows him to use high doses of radiation to very precisely target and destroy the smallest of cancer lesions in the brain without damaging normal brain cells. The treatment uses 90 to 100 X-ray beams that converge at a single spot. Individually, each beam is weak, but the beams cross and converge at the site of the cancer and provide a lethal full dose of radiation to strike the cancer—and only the cancer. Kleinberg says that improved imaging technologies have made it easier to detect and treat spots of brain metastasis as soon they occur, even those seeded deep within the brain. He says the ability to detect and safely treat very early spread to the brain is the key to preserving brain function.

“Before we had radiosurgery, we had to treat the entire brain with radiation and that, of course, caused many side effects,” says Kleinberg. “Now, in most situations, we can actually treat very small areas of the brain with almost no side effects.” He says an added advantage to the less toxic treatment is that patients can continue to receive chemotherapy at the same time, helping to keep the spreading cancer in check.

Kleinberg and the Kimmel Cancer Center radiosurgery team offer one of the very few treatment options for patients with spread of cancer to the brain. He recalls very clearly the first patient he ever treated with this approach, a wife and mother of a young child. He gave her four treatments over four years to eliminate new areas of cancer that had spread to her brain. The cancer had spread throughout her body, and it ultimately claimed her life. Kleinberg’s treatment extended her survival, and by keeping the brain metastases in check, the woman accomplished things she didn’t think were possible. She went back to school and earned her graduate degree and, most importantly, she was able to remain fully engaged with her child.

Kleinberg saw the patient’s husband several years later, and he recounted to him how grateful his wife was for the treatment and the gift of additional time with her daughter and husband—and a fully functional mind to her last day.

He has also used radiosurgery to revolutionize the treatment of another type of brain tumor known as acoustic neuromas. This type of tumor is not directly life threatening, but it can severely diminish quality of life.

Acoustic neuromas develop and wrap around the main nerve that leads from the inner ear to the brain. As they grow, they exert pressure on the brain and can cause hearing loss in the affected ear. Traditional surgery can remove the tumor, but cutting through nerves is almost always required and cause permanent hearing loss and sometimes facial deformity. Patients suffer balance problems, facial pain, headaches displacement from jobs and recreational activities that require hearing, and many times become depressed. For some patients, there is an alternative. Kleinberg uses a radiosurgery technique developed by experts in the Department of Radiation Oncology and Molecular Radiation Sciences. “Maybe we can make the standard care—which is radiation therapy and testosterone-blocking hormone therapy—better by introducing short pulses of testosterone to sensitize prostate cancer cells just when we need to.”

The priming strategy is a targeted treatment that affects only prostate cancer cells and prostate tissue. Yegnasubramanian is also developing a test to determine if the treatment is working, using blood and urine samples to determine the methylation pattern of patients’ prostate cancer genes. “After the patient receives radiation treatment, if cancer cells were killed, the amount of abnormally methylated cancer-specific DNA should go down,” he says. “This will tell us if cancer cells are dying off or are not dying off. If the methylation pattern is still high, it tells us we need to try a different treatment.”
breast cancer expert Richard Zellars proved that small changes can make a big difference. In the quest for new drugs and technologies, he showed that sometimes experts have all the tools they need to make advances. The difference is made in how they choose to use these tools.

Zellars saw such an opportunity in breast cancer and seized it. It didn’t matter that his idea to combine radiation therapy with chemotherapy was rejected by nearly every expert. He believed in it, and no one was going to change his mind. “There wasn’t one expert who thought it could be done,” says DeWeese, “but Rich said ‘I know we can do it,’ and he transformed how women with breast cancer are managed.”

There was plenty of evidence that patients with other cancers, including lung, rectum, sarcoma, head and neck, and esophageal cancers, responded better to combined treatments with chemotherapy and radiation. He wanted the same benefits for his patients. The limiting factor was burns. Chemotherapy makes the skin more sensitive to radiation, and in a European study of women who had radiation of the whole breast, almost half suffered severe burns. When doctors attempted to treat the breast and lymph nodes, the burn rate increased to about 90 percent.

The standard of care had been consecutive treatments with four to six months of chemotherapy, followed by a month of radiation treatment. Not surprisingly, every other expert had abandoned the prospect of combined therapy despite its potential therapeutic benefits; the side effects made it impossible—or so they thought. Zellars remained determined.

When he began his research about 10 years ago, partial breast radiation was gaining in popularity, and that sparked an idea. When he looked back at the European study he found the clue that helped him adapt combined therapy to breast cancer. In the study, researchers reported that when they increased the volume of breast treated, burns also increased. Maybe then, Zellars hypothesized, the opposite would also be true. If the volume of breast treated was decreased, the occurrence of burns would decrease. The only way to know for sure would be to try it in patients. It was risky for sure, but he was able to get approval for a smaller-volume treatment.
for a clinical study combining chemotherapy and partial breast radiation.

Zellars expected that about 20 percent of women would still be at risk of burns, so he planned to use partial breast irradiation to precisely target their tumors and follow them closely so that radiation treatment could be stopped if there were signs of burns.

The results shocked everyone. There were no burns. Toxicities with Zellars’ treatment were lower than treatment with radiation alone. “In medicine this is what we call a homerun,” says Zellars. To confirm its safety, he continued to test the therapy in combination with a wide variety of drugs, including those most likely to cause burns. Still, none occurred.

The study, which was funded by the Breast Cancer Research Foundation, also confirmed Zellars’ hunch that there were therapeutic benefits to the combined therapy. Eighteen of his patients treated, had one of the worst types of breast cancer, a treatment-resistant form known as triple negative breast cancer. Several published studies were reporting unfavorable results in patients who received partial breast irradiation and chemotherapy, but Zellars’ patients were doing well. None had suffered the cancer recurrences other researchers were reporting. The difference was in Zellar’s unique approach. The Kimmel Cancer Center was the only place giving partial breast irradiation and chemotherapy together. In the other studies, the women received the treatments one after the other. The difference was in the delivery.

To confirm these results, Zellars is leading a larger, 120-patient study in collaboration with Kimmel Cancer Center medical oncologists and other Johns Hopkins clinics and hospitals, including Green Spring Station Healthcare and Surgery Center, Sibley Memorial Hospital and Suburban Hospital, as well as Anne Arundel Medical Center, and York and Reading hospitals in Pennsylvania. “If we can confirm these findings in larger studies, it could mean a big advantage for these patients,” says Zellars. Triple-negative breast cancers account for approximately 15 to 20 percent of breast cancers, and these patients have limited treatment options, he says. They are not influenced by hormones, so they do not respond to popular hormone-blocking treatments like tamoxifen.

Ten years and three studies later Zellars calls it a defining moment. By adjusting the way treatment is given, he has decreased toxicities and length of treatment for many breast cancer patients and possibly made much-needed progress against one of the most difficult forms of the disease.

**Safety First**
**Mapping the Brain**

As a pediatric radiation oncology expert, Stephanie Terezakis specializes in treating the youngest of cancer patients, so safety and toxicities take on even greater meaning to her. “Our patients may live another, 50, 60, or 70 years, so we think more about safety and long-term survivorship,” she says.

Brain cancers are the most common solid tumor in children, so one of Terezakis’ primary focuses is gaining a more complete understanding of the effects of radiation on the brains of pediatric patients. “Radiation to the brain can cause significant learning and cognitive deficits in children,” says Terezakis. But different parts of the brain control different functions, and she wanted to learn more about the specific damages that occurred in hopes of identifying ways to protect children.

To study the impact of radiation on brain development, pediatric patients were followed for more than two years with neuropsychological testing—tasks that measure a psychological function linked to a specific part of the brain—and functional brain MRIs, which measure brain activity. She used the tests to observe and document changes to brain tissue and function in relationship to radiation doses and the amount of brain treated. “We found clear correlations between increased radiation dose and decrease in volume of normal brain tissue in areas that control memory, concentration, and verbal language skills,” says Terezakis. When functional brain MRIs of patients were compared to MRIs of healthy children who had never received radiation, Terezakis, not surprisingly, found distinct differences.

Much of the neuroscience on radiation and brain impact comes from laboratory models that do not align with how radiation is actually delivered. The next step involves a collaborative study using a unique mouse behavior model to more closely replicate real patients undergoing radiation treatment.

Terezakis also recognizes that brain tumors, independent of radiation treatment, inflict damage on the brain. To distinguish developmental impact caused by the tumor from the impact of radiation treatment, she is comparing brain tumor patients who have been radiated to brain tumor patients who

“Curing the cancer remains our priority, but these data allow us to do it in a smarter way. Now, hopefully we can cure the patient and minimize long-term side effects.” —STEPHANIE TEREZAKIS
never received radiation and those who were treated only with surgery to accurately relate differences in development to their causes.

With all of this data in hand, her goal is to develop a map of the brain that would relate dose of radiation to impact on specific areas of the brain. The map would show the maximum dose of radiation that each area of the brain could tolerate without causing functional deficits. Terezakis suspects she and her research team will find that some areas will require smaller doses, but other areas may be able to safely tolerate increased doses.

“Curing the cancer remains our priority, but these data allow us to do it in a smarter way,” says Terezakis. “Now, hopefully we can cure the patient and minimize long-term side effects.”

QA Tool
Radiation therapy is an effective and safe staple of cancer treatment, but she says the multistep complexity of radiation therapy, and the numerous precision measurements its use entails, requires a higher level of safety analysis.

Working with researchers at Washington University in St. Louis, Terezakis and team focused their attention on potential “near-miss” events and determined that a combination of approximately six common quality assurance (QA) measures, including use of hardware built into many radiotherapy-delivery machines and a relatively simple checklist, could prevent more than 90 percent of the potential incidents. The checklist includes reviews of patient charts before treatment by both physicians and the radiation-physicists who calculate the right dose of radiation. It also includes a mandatory “timeout” by the radiation therapist before radiation is turned on to double-check that the written treatment plan and doses match the radiation delivery machines. “While clinicians in this field may be familiar with these quality assurance procedures, they may not have appreciated how effective they are in combination,” says Terezakis.

In ongoing research, she found that patients with larger tumors, more complex treatment plans or suffering from pain were characteristics most predictive of near misses and potential incidents. Terezakis says the newly identified variables will help clinicians recognize patients who may require a higher level of quality assurances.
Focused Radiation Stimulates Cancer Immunity

The prevailing opinion in cancer research was that chemotherapy and radiation therapy suppressed the immune system, but radiation oncology resident Andrew Sharabi proved that creative thinking and a fresh perspective sometimes trumps experience.

“We’re finding that focused radiation, like what is used in stereotactic radiosurgery, may actually stimulate an immune response,” says Sharabi. He is collaborating with Kimmel Cancer Center cancer immunology expert Charles Drake to decipher how to harness this power to improve cancer treatment.

Before there were prodrugs, radiolabeled nanoparticles, or proton beams, sophisticated machines that delivered targeted X-ray beams with complex and precise trajectory calculated by skilled physicists were a mainstay of cancer therapy. They remain so today but are better and safer and just part of a cadre of technologies and biologic therapies radiation oncologists, physicists, and molecular scientists use to fight cancer. Radiation Oncology and Molecular Radiation Sciences seamlessly unites physics, engineering and medicine to plan and deliver care that is based on the biologic underpinnings of cancer. Advances in our understanding of radiation biology, molecular biology, and imaging are resulting in unique radiation oncology treatment strategies never before imagined, and these innovations are allowing our scientists to see, study, and treat tumors in completely new ways.
He recently presented his research at the annual meeting of the American Society of Therapeutic Radiation Oncology (ASTRO). His research was selected from thousands of submissions as the featured presentation at the meeting, making him the first resident ever to receive the honor and the first basic science research to be highlighted at the meeting in over a decade.

Drake was the ideal mentor for Sharabi. He was part of a research team that recently reported a two-pronged immune therapy approach coupled with targeted radiation treatment significantly prolonged the life of the mice with glioblastoma brain cancer. The study found the treatment also protected the mice from new tumors.

Sharabi, too, was employing a novel mouse model for his studies. He used mice with tumors on each side. One side was shielded from radiation, and the other side was treated with radiosurgery using John Wong’s small animal research platform. Not surprisingly, tumors that were treated with radiosurgery were destroyed, but when the mice also received and immune therapy drug in their chow, tumors on the side not treated with radiation also responded. “Radiation therapy has always been thought of as a localized treatment,” says Sharabi. “But when we combine radiosurgery with immune therapy it gains an added systemic activity.”

Sharabi suspects that cell damage invoked by radiation to the tumor causes cancer cells to present antigens—molecules that induce an immune response—on their surface. But, that’s not enough to activate an attack against cancer cells. Sharabi says tumors also generate regulatory cells that shield cancers from an immune response. This tug of war leaves the immune system in neutral, ready and poised to attack but awaiting a signal to act.

To flip the switch, Sharabi employed a novel new type of immune treatment, known as immune blockade therapy. Pioneered by Kimmel Cancer Center immunology experts, it was the same type of approach Drake took in the brain cancer studies. Immune blockades prevent cancer cells from deploying immune dampening regulatory cells. With regulatory cells taken care of, he could use radiosurgery to enlist an entire complement of immune cells to fight the cancer—killer T cells that, as the name implies, kill cells; memory T cells that remember the tumor cells and have the power to keep the cancer in check indefinitely, and B cells, which generate antitumor antibodies that interfere with cancer cells’ DNA and stop them from replicating new copies.

When Sharabi removed the tumors from the mice and looked inside, what he saw provided an even greater insight into cancer’s immune regulatory actions and how they are influenced by radiation. Most of the time when researchers look inside of tumors, they don’t find immune cells. “The immune system is shut out,” says Drake. “It has been a vexing problem in immune therapies.” Yet, when Sharabi looked inside the mouse tumors that had been radiated, he found an increased number of tumor infiltrating lymphocytes, a type of white blood cell involved in killing tumor cells and typically associated with better outcomes. “We suspect that tumors, which are typically hard, become softer when they are radiated. So something happens—either cell death or a breakdown of the vasculature—that allows other cells to get in,” says Sharabi. “Radiation opens the door, and blockade therapy allows the immune cells to go to work.”

To move these promising findings closer to clinical studies, Sharabi plans to study head and neck cancer patients.
receiving radiosurgery. He will collect blood samples before, during, and after the radiation treatment and use them to measure and quantify the immune response it activates. He also plans to study the addition of immune blockade therapy in cancers, such as prostate, head and neck and early lung cancers, that can be cured with radiosurgery. "Adding immune therapy in these cancers may give us even better control," says Sharabi. "It essentially makes a vaccine out of the tumor." The blood-based research will also facilitate identification of biomarkers that can be used to identify patients most likely to benefit and to monitor treatment responses.

Sharabi sees great potential for the combined radiosurgery/immune therapy approach. He wonders if radiation could be used explicitly to incite an immune response. "We could give radiation to patients, not necessarily because they need it for local control of a tumor, but specifically to engage the immune system," says Sharabi. "Using radiation to shift the tide of immune cells in our favor and immune therapy to remove the brakes on the immune response could deliver better responses against a wide variety of cancers, even advanced cancers."

Theranostics, Aptamers, and Nanoparticles
In a new approach dubbed "theranostics" because it combines the diagnostic properties of molecular imaging with cancer therapy, a multidisciplinary team of experts, including Radiation Oncology Director Ted DeWeese, and cancer imaging experts Martin Pomper and Zhaver Bhujwalla, developed an idea that takes advantage of important molecular components of cancer and allows researchers and clinicians to see inside the cancer cell and view them as they are being treated. The team is developing ultra-tiny structures called nanoparticles filled with an anticancer drug that also sensitzes cancer cells to radiation and a radiopharmaceutical or cell-imaging agent. The nanoparticle is targeted to PMSA, a biomarker for prostate cancer, so that it zeroes in on and delivers its anticancer payload specifically to prostate tumors. The particle is labeled with a radioactive isotope, which can be imaged or used to treat cancer. It is given intravenously so that it can attack cells growing anywhere in the body.

In other work, DeWeese and prostate cancer researcher Shawn Lupold became the first to show that small inhibitory RNA (siRNA) could be used for cancer therapy. This breakthrough research focuses on siRNA, small molecules that have the ability to interfere with the expression of genes. DeWeese and team used aptamers, a guidance system of sorts, to get the RNA molecule to its target inside of cancer cells where it shuts down cancer cells’ ability to repair the injury that radiation inflicts, and as a result, they die. The aptamers, which allow the repair-blocking inhibitory molecules to be targeted specifically to cancer cells, are unique to Johns Hopkins and considered the gold standard. Moreover, it is a platform technology that can be used not only for prostate cancer but any cancer type, simply by changing the aptamer.

Another nanotech approach DeWeese is exploring for prostate cancer treatment uses alpha particles, a type of radium isotope, that are naturally targeted to the bone, where prostate cancer most often spreads. It captures the killing power of decaying radium, but in this form it has a short life of about ten days and only causes damage in the limited path it travels in the body. Radium has a chemical relationship to calcium, and so acts in the human body like calcium, naturally traveling to the bone. Investigators are studying a combined nanoparticle/alpha particle/radiation treatment. The nanoparticle, loaded with its radiation-sensitizing anticancer drug, is given simultaneously with the bone-metastasis-targeting alpha particle to exquisitely and precisely attack prostate cancer and its spread.

Change the Environment, Change the Tumor
About one-third of patients diagnosed with non-small cell lung cancer, the most common type of lung cancer, have cancers that have begun to spread outside the lung to lymph nodes in the chest. The best opportunity to cure patients is when they are first diagnosed, but using the best radiation and drug therapies available today, one quarter to one half of patients have their cancers come back. At that point there are very few treatment options. Radiation oncologist and lung cancer expert Russell Hales is determined to change these statistics.

“I tell my patients, if we are going to cure your cancer, we need to win two battles. First, we have to get rid of the primary tumor in your chest, and then we have to stop the tumor from spreading,” says Hales. It is not an either-or proposition, he says. If the tumor spreads to the bone, the patient cannot be cured, but if it comes back locally in the chest, it can still claim the patient’s life. To shift the battle in the patient’s favor, Hales is looking to a cancer pathway called Hedgehog. It is a primitive development pathway that cancer cells hijack to maintain survival. “When tumors are breaking the rules to divide, grow, and spread, they use this pathway,” says Hales. He believes drugs that block Hedgehog may make radiation treatment work better in patients with this locally advanced form of lung cancer.

When Hales and team turned off Hedgehog in test tube laboratory models, tumor cells didn’t grow, indicating the gene was a key player in at least some lung cancers. When he added radiation to the mix, he expected to see the cell kill go up. It didn’t. “With or
RadVision is a treatment for prostate cancer where seeds are placed and multiple X-rays are taken. This is fed into a computer to generate a three-dimensional arrangement of seeds. The positions are then superimposed over ultrasound images to guide the placement of additional seeds.

without Hedgehog inhibitors, the cell kill was essentially identical,” says Hales. “This was not what we expected to see.” He could have scrapped the project at this point and deemed it a failure, but his persistence proves that as much knowledge is gained from what doesn’t work as what does. Looking back, he could not have predicted the direction the seemingly ill-fated project would take. “We were staunch in our hypothesis that tumor cells control Hedgehog,” says Hales. “We were surprised to find that isn’t what happens, but that’s the beauty of science.”

Test tubes are not the same as the human environment, so Hales decided to take another look using mouse models designed that more closely match human tumors. Tumors do not occur in isolation as in the test tube model. Rather they occur in an environment of other normal cells. Hales wanted to find what affect these other cells had on the tumor, so he used medical physicist John Wong’s small animal research platform invention, a linear accelerator with onboard CT scanner scaled down in size for animal research to find out. The imaging capability allowed him to look more closely at the stroma, the supportive cells surrounding and nourishing the tumor.

What he found confirmed his laboratory studies. Blocking the Hedgehog pathway did not directly do anything to the tumor. Instead, it stabilized the blood cells in the stroma around it, allowing more oxygen to get in the tumor—an essential component for radiation therapy to work. “A tumor that does not have a good supply of oxygen is difficult to radiate. It is a radiation oncologist’s nightmare,” says Hales. He is continuing to study the mechanisms to understand precisely how Hedgehog collaborates with stroma cells to promote cancer growth and, if he can secure funding, will advance to patient studies. “If more studies prove these findings correct, we now have a the first targeted radiosensitizer out there and one that works differently than every other targeted therapy,” says Hales. “Other targeted therapies go after alterations in the tumor cells. Our targeted therapy works by targeting the cells around the tumor. That means it could work against almost any cancer type.”

Seeding a Cure
Brachytherapy is a widely used and promising tool of radiation therapy and commonly used in the treatment of prostate cancer as an alternative to surgical removal of the prostate. Radiation is delivered to the prostate via tiny seeds about the size of a grain of rice. Accurate placement of these seeds has been the biggest challenge, but brachytherapy expert Danny Song has been a leader in pioneering guidance systems that ensure the seeds are deployed where they should.

To destroy prostate cancer, about 50 to 100 seeds are placed by needle in the prostate while the patient is under general anesthesia. The greatest limitation to brachytherapy, Song says, was that
Bad Timing

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. This process, the one that 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.

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 is 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 lung, prostate, liver, and bladder cancers. By incorporating luciferase, the gene in fireflies that causes their iconic glow, into the model Tran and team are able to make all of genes related to EMT glow in the mice. Now, they can test drugs that could inhibit EMT and see the impact on all of the genes in its pathway. If they can inhibit the gene, perhaps they can sensitize resistant cancers to radiation treatment and anticancer drugs. To test this, Tran is using the small animal model research platform (SARRP), a miniature radiosurgery machine where he can evaluate the effectiveness of potential drugs in a real radiation treatment environment and distinguish promising agents that warrant further studies from agents that do not work.

When Tran is not working on his EMT research, he is searching for other ways to sensitize cancers to radiation therapy. He approaches the task like a detective, sleuthing out the unique instincts of the cancer cell. Like any good investigator, Tran has created a profile of his villain. “Cancer is good at doing bad things, but it has certain things that it needs. We need to figure out what these needs are and block them,” says Tran. 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. He is working with radiology and radiological science researcher Venu Raman on studies of a drug that block the gene.

As a clinician and a laboratory scientist, Tran says he appreciates the value of basic science, but at the same time, he treats patients, some who are not doing well, and he recognizes the urgency of translating laboratory discoveries into patient care. “It makes me impatient,” he says. “I have a lot of optimism because of the unique tools and talent we have at the Kimmel Cancer Center. I want to use this talent and these tools to get promising new therapies to patients more quickly.”
Funding the Cure

Brachytherapy expert Danny Song received vital support for his RadVision seed placement guidance system through the continued generous support of a grateful patient. John and Pembroke Noble began supporting Song’s work in 2009, with several generous gifts. Subsequently, the couple named Johns Hopkins University the beneficiary of a $1.1 million IRA bequest to establish the John and Pembroke France Noble Fund for Oncology Research. The fund will support Song’s clinical research and advance other radiation oncology research projects. “We heard about Dr. Song’s work and wanted to help,” says Mr. Noble. His ties to Johns Hopkins go beyond his treatment. His wife Pembroke is the great great niece of its benefactor Johns Hopkins. Mr. Noble says he shares his wife’s appreciation of the advances being made at the Kimmel Cancer Center and throughout Johns Hopkins Medicine. “Johns Hopkins is the place to come if you are sick, and it was the place we wanted to sup port,” says Mr. Noble.

What is a Bequest?

A bequest is a type of gift that has no cost to the donor during his or her lifetime. It can be created by including Johns Hopkins as a beneficiary in a will, retirement plan, or life insurance policy. Designating a retirement plan, such as an IRA, 401(k), or 403(b) is an easy way to make a bequest, but one of which many people are unaware. Retirement plan bequests can be made by naming Johns Hopkins as a whole or partial successor beneficiary on the retirement plan’s form and sending a copy to the Johns Hopkins Office of Gift Planning.

Such gifts ensure the future strength of Johns Hopkins, while still allowing the donor to continue to take withdrawals from the plan during his or her lifetime. A gift of retirement assets to Johns Hopkins is exempt from federal estate and income tax, but retirement funds left to individual heirs can get levied with heavy income tax and estate taxes.

Individuals who make a bequest commitment or life-income gift are welcomed into the Johns Hopkins Legacy Society. For more information, visit https://rising.jhu.edu/giftplanning, or contact the Johns Hopkins Office of Gift Planning at 800.548-1268 or giftplanning@jhu.edu.

there was no good, real-time way to see if the seeds were getting to correct place. “X-rays show the seeds but do not provide a clear image of the prostate, and ultrasound shows the prostate well, but not the seeds,” Song says.

He decided to combine the two technologies into one. Through a collaboration with Johns Hopkins University engineers and funding from the John and Pembroke France Noble Fund for Oncology Research, and the Department of Defense, Song developed RadVision. As seeds are placed, multiple X-rays are taken and fed into a computer to generate a three-dimensional arrangement of seeds. The seed positions are then superimposed over ultrasound images to guide the placement of additional seeds.

Song compares other methods of seed placement to driving with an outdated GPS. The result could be too many seeds in one place and the potential of excessive radiation and damage to other organs such as the rectum or urethra, or as detrimental, not enough seeds to adequately destroy the cancer. RadVision, on the other hand, provides real time updates and guidance. “Now we’re getting updated maps, traffic information, and even accident information that tells us to revise our route,” says Song.

RadVision received FDA approval after a National Institutes of Health-funded clinical study in 80 patients that proved it provided the most accurate seed placement. In the past patients who have received brachytherapy also required external beam radiation to compensate for inadequate seed placement. Song says seed placement with RadVision is so accurate, it may eliminate the need for additional radiation treatments, saving patients the risk of additional side effects, time, and money. Larger studies are being planned.
A urine-based test for early detection and monitoring of bladder cancer and nanoparticles that can deliver chemotherapy drugs to bladder tissue are among the first projects awarded research grants by the Johns Hopkins Greenberg Bladder Cancer Institute. The institute, which aims to develop new clinical strategies for combating bladder cancer through intensive, collaborative and innovative research, awards grants of up to $50,000 each year to encourage young investigators to take on research that advances the science and treatment of bladder cancer and to leverage existing resources and expertise.

“We’re very excited about these projects, which potentially could lead to novel therapies for bladder cancer, or to optimizing and characterizing existing therapies and improving their efficacy,” says William B. Isaacs, Ph.D., a genitourinary cancer expert and interim director of the Greenberg Institute.

The Johns Hopkins Greenberg Bladder Cancer Institute was established in May 2014, with a $15 million gift from Baltimore-area commercial real estate developer Erwin L. Greenberg and his wife, Stephanie Cooper Greenberg, along with a $30 million investment from The Johns Hopkins University.

The institute is the first of its kind in the world dedicated to advancing the scientific understanding of bladder cancer and improving its treatment. Its experts include multidisciplinary research teams from the Johns Hopkins Kimmel Cancer Center and faculty from the Johns Hopkins University School of Medicine’s Department of Radiation Oncology and Molecular Radiation Sciences, the James Buchanan Brady Urological Institute of The Johns Hopkins Hospital, and Johns Hopkins’ departments of Pathology and Surgery.

“Drawing upon the extraordinary resources available at Johns Hopkins and working with physicians at other world-class centers, the institute will continuously and rapidly elevate the state of the science in bladder cancer, moving ever closer toward the goals of preventing, effectively treating, and ultimately curing bladder cancer,” says Erwin Greenberg.
The 2014 awardees and projects:

**Trinity Bivalacqua, M.D., Ph.D.:**
Bivalacqua’s project will investigate the development of nonadhesive, biodegradable nanoparticles loaded with chemotherapy and other solutions. His team will compare the effectiveness of these nanoparticles with standard ways of delivering chemotherapy in a mouse model of bladder cancer to determine whether nanoparticles better sustain delivery of chemotherapy into bladder tissue, preventing tumor recurrence and progression.

**Charles Drake, M.D., Ph.D.:**
This study involves a catalogue of the sequences of RNA—strings of chemical letters that form the “readout” of DNA and help construct proteins—from bladder cancer samples of people with advanced disease. Drake’s goal is to identify new and existing molecules on the surface of lymphocytes—white blood cells that penetrate tumors and kill cancer cells—that regulate how the immune system identifies and marks cancer cells for destruction. The findings could lead to discovery of new targets for cancer immunotherapy.

**George Netto, M.D.:**
Netto will continue work on a noninvasive, urine-based test to identify mutations in the “on/off switch” of a gene called telomerase reverse transcriptase (TERT), which is present in a range of bladder cancer precursor lesions. New experiments will determine how well a test for TERT mutations can detect bladder cancer in urine samples of individuals at high risk for bladder cancer, determine the utility of detecting TERT mutations among urine samples taken during follow-up of bladder cancer patients to monitor disease recurrence, and see if it is worth expanding the test to include additional genetic mutations found in bladder cancer.

**Peter H. O’Donnell, M.D.:**
This study will test whether progressing bladder cancers acquire mutations that may activate and expand the number of tumor-infiltrating T lymphocytes (TILs)—white blood cells found in tumors that kill cancer cells. Investigators will look for genetic changes in TILs that predict robustness of immune responses against bladder cancer to see if they contribute to better recurrence-free and overall survival.

**Armine Smith, M.D.:**
This animal study will explore stimulation of a protein called TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), which kick starts the process of cell death, as a potential way to increase the effectiveness of BCG (Bacillus Calmette-Guerin), the main biological treatment for nonmuscle invasive bladder cancer. Investigators also will collect tissue from patients with bladder cancer to identify levels of TRAIL receptors before and after BCG treatment, then correlate them with treatment outcomes.

**Dan Theodorescu, M.D., Ph.D.:**
His research will investigate the role of AGL, an enzyme that suppresses bladder tumor growth. Patients with metastatic bladder cancer have lower levels of AGL. Scientists will track levels of AGL and another enzyme called HAS2 to determine their correlation with patient outcomes. The researchers also will study mice that do not express AGL to see if they are more susceptible to bladder cancer.
Tobacco use and exposure has been linked to oral-cancer causing infection with the human papillomavirus type 16 (HPV16).

Earlier work by the Kimmel Cancer Center/Bloomberg School of Public Health research team linked HPV16 infection through oral sex with 80 percent of cancers of the mouth and throat. Lead researchers Carole Fakhry, M.D., M.P.H., and Gypsyamber D’Souza, Ph.D., M.S., M.P.H., were seeking to reconcile the common practice of oral sex with the low rates of HPV-positive oral cancers. “We knew there must be co-factors in the process that explain why some people develop persistent HPV16 infections and HPV-positive oropharyngeal cancers when most other people don’t,” says D’Souza, associate professor of epidemiology. “It appears that tobacco exposure increases the likelihood of having oral HPV16 infection, and although we do not yet know why, we suspect that the virus may not be cleared from the body as easily in people who use tobacco.”

Previous studies have shown an association between oral HPV16 infection and cigarette use. The latest study expanded upon this work by considering all tobacco exposure, even secondhand smoke. The researchers emphasize that tobacco use and exposure increase the risk—but do not directly cause—HPV16 infection. Nonsmokers can become infected with HPV16.

The study results suggest that even modest amounts of tobacco use are associated with higher oral HPV prevalence,” says Carole Fakhry, M.D., M.P.H., assistant professor of otolaryngology-head and neck surgery. “It may provide an additional reason for smoking cessation.”

The research was funded by the National Institute of Dental and Craniofacial Research (P50 DE019032, R01 DE021395, R01 DE023175), the Milton J. Dance, Jr., Head and Neck Center at Greater Baltimore Medical Center, and Merck.

In a study of 92 fully matched bone marrow transplant patients who received the shortened treatment, about half developed GVHD, which is about the same results obtained with the longer standard immunosuppressive treatment. However, the percentage of patients with the chronic form of GVHD were drastically lower than seen with the standard treatment.

“Reducing the post-transplantation treatment allows for the earlier integration of other treatments.”

Specifically the shortened regimen includes pre-transplant treatment with two chemotherapy drugs that wipe out patients’ immune systems and prepare their bodies to accept the donated bone marrow. After the transplant, patients receive the two-day course of cyclophosphamide. “Reducing the post-transplantation treatment allows for the earlier integration of other treatments,” says Christopher Kanakry, M.D., who collaborated with Luznik on the study. “With immunosuppressive therapies stopped earlier, immune-based treatments to go after any remaining cancer could be started much sooner.”

This work builds upon earlier studies successfully using cyclophosphamide to stave off severe GVHD in patients receiving bone marrow from half-matched donors. Additional clinical studies are planned.

The research was funded by Otsuka Pharmaceutical.
A genetic analysis of more than 87,000 men—43,303 with prostate cancer and 43,737 without—by a global team of scientists has revealed 23 new differences in the genetic code that could increase a man's risk of developing the cancer. The analysis is believed to be the largest of its kind and has uncovered genetic mutations linked to prostate cancer risk among men from a broad array of ethnic groups, including European, African, Japanese, and Latino ancestry.

William Isaacs, Ph.D., a genetic scientist at the Brady Urological Institute, says the analysis represents a conglomeration of information gleaned from many smaller studies over time. For its part, Johns Hopkins scientists, Isaacs and the institute's director, Alan Partin, M.D., Ph.D., contributed samples and data from 800 African-American men—half with prostate cancer and half without.

The analysis, which was led by the Institute of Cancer Research, the Royal Marsden National Health Services Foundation Trust in London, and the University of Southern California, scanned 10 million areas of the genome to identify single differences in the A-T-C-G genetic code, called SNPs (pronounced snips). It is the most common type of genetic variation. The investigators uncovered the 23 new SNPs by comparing the scanned genetic regions of men with prostate cancer to the cancer-free men.

“There is power in numbers that helped us find new variants that were only hinted at in smaller study populations, especially among minority men. As we found the same variants across several populations, the evidence became stronger that they were definitely linked to prostate cancer,” Isaacs says.

Inheriting any single genetic variant has a small effect on genetic risk, but Partin says some men will inherit many of these variants, which could put them at substantially higher risk for prostate cancer—three to six times higher than the general population. Knowing what these genetic variants are—76 previously discovered and these additional 23—will help identify men who could benefit from early prostate cancer screening, he says.

The research was funded by the U.S. Department of Defense, the National Institutes of Health’s National Cancer Institute, Cancer Research UK, Prostate Cancer UK, Patrick Henry, P. Kevin Jaffee, and the Peter Jay Sharp Foundation.
How Breast Cancer Spreads
*Science Translational Medicine, Aug. 13, 2014*

Breast cancer cells can lay the groundwork for their own spread throughout the body by coaxing lymphatic cells, called LECs, to send out tumor-welcoming signals. The research team found these signaling molecules released by breast cancer cells in animal and cell culture laboratory experiments.

It appears that the molecules set a multistep cellular process in motion that beckons tumor cells to the lungs and lymph nodes while also increasing and altering blood vessel formation that make it easier for tumor cells to travel to and infiltrate the lungs.

“It was surprising to find that LECs can play such an active and significant role in tumor spread,” says **Aleksander Popel, Ph.D.**, professor of biomedical engineering and oncology and member of the Kimmel Cancer Center. “Conventionally, lymphatic vessels were regarded mainly as passive conduits through which tumor cells spread from the primary tumor site. Now we know that they enable metastasis and that they may even play an important role in whether or not immune cells recognize and attack cancer.”

Popel and team identified an FDA-approved antiviral drug used to treat HIV that can block this molecular signaling process. In animal and test tube studies, it successfully blocked cancer cell spread. The researchers say combining the antiviral drug with another drug to block the blood vessel changes provides a potential way to prevent breast cancer spread in humans. “It could be delivered along with chemotherapy right after surgical removal of the tumor in a bid to prevent any leftover circulating tumor cells from finding a new niche in the body,” says Popel.

Popel collaborated with Kimmel Cancer Center bioinformatics expert **Elana Fertig, Ph.D.**, and breast cancer researchers **Kideok Jin, Ph.D.**, and **Saraswati Sukumar, Ph.D.**, on this study.

*The research was funded by the National Institutes of Health (ROI CA138264) and the Safeway Foundation for Breast Cancer.*

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Cancer-Fighting Bacteria
*Science Translational Medicine, Aug. 13, 2014*

A modified version of the bacterium *Clostridium novyi* (*C. novyi-NT*) produced a strong and precisely targeted antitumor response in studies of animals and humans.

The bacteria thrive in oxygen-poor environments, making it ideal for treatment of oxygen-depleted areas of tumors where radiation therapy and chemotherapy do not work well. To make it safe for therapy, the Kimmel Cancer Center scientists engineered the bacteria to remove its toxin-producing genes.

Researchers tested the bacteria-based treatment in 16 pet dogs being treated by veterinarians for naturally occurring tumors. Six of the dogs had some response, including three that had complete eradication of their tumors.

An MD Anderson Cancer Center patient with an advanced soft tissue tumor in her abdomen received a direct injection of the bacteria spores in a tumor that had spread to her shoulder and experienced a significant reduction of the tumor in and around the bone. Doctors are encouraged by the patient’s response but say they have not treated enough people to be sure if the same spectrum of responses observed in dogs will translate to humans. However, they say dogs provide a good glimpse into what may happen in humans because they develop tumors spontaneously and are treated with many of the same cancer drugs.

Researchers also tested the bacteria injection in rats with implanted human glioma brain cancer cells. The treatment killed tumor cells and spared surrounding normal cells while also extending survival.

The study of the bacteria treatment in humans is ongoing. “One advantage of using bacteria to treat cancer is you can modify these bacteria relatively easy to equip them with other therapeutic agents, or to make them less toxic, as we have done here,” says **Shibin Zhou, M.D., Ph.D.**, director of experimental therapeutics at the Kimmel Cancer Center’s Ludwig Center for Cancer Genetics and Therapeutics. He and his colleagues began exploring *C. novyi-NT*’s cancer fighting potential a decade ago after reading 100-year-old accounts of patients who experienced cancer remissions subsequent to serious bacterial infections. Zhou says an added advantage to the bacteria therapy is that infected tumors should also generate a strong immune response against cancer cells.
cumulates when cells are deprived of oxygen and that stimulates the formation of new blood vessels that deliver the oxygen and nutrients that cells need to survive. Since more cells require more oxygen, HIF-1alpha also blocks cell division by preventing cells from replicating their DNA. Cancer cells want HIF-1alpha around to stimulate blood vessel growth—except when they want to divide.

How do cancer cells accomplish these seemingly incompatible tasks? Maimon Hubbi, Ph.D., a postdoctoral researcher in Semenza’s lab, found that cancer cells use two proteins that have long been known to control cell growth. Cdk2, a protein that suddenly appears just before cells begin to replicate their DNA, attaches to HIF-1alpha and causes its destruction. Once cells finish replicating their DNA, Cdk2 is itself destroyed and replaced by Cdk1, which also attaches itself to HIF-1alpha but has the opposite effect: Cdk1 protects HIF-1alpha from destruction and increases its ability to stimulate blood vessel growth. Several drugs that inactivate Cdk1—and cause HIF-1alpha destruction—are currently being tested as anti-cancer agents in clinical trials.

How Cancer Cells Keep Going When Other Cells Stop
Proceedings of the National Academy of Sciences, July 28, 2014

Researchers have uncovered another way that cancer cells subvert normal cellular processes to maintain their unchecked growth. Most normal cells do not divide unless there is enough oxygen around to support additional cells, but many cancer cells continue to divide even when oxygen is in short supply.

Two decades ago, Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of pediatrics, medicine, oncology, radiation oncology, biological chemistry and genetic medicine, discovered HIF-1alpha, a protein that ac-

Recruiting Cancer Immunity
PLOS One, July 11, 2014

A three-part treatment of glioblastoma brain cancer in animal models successfully generated an immune response and increased survival time. The treatment involves a novel combination of three existing therapies. They are highly focused radiation therapy and two types of immune therapies—one that mobilizes immune cells and another that removes protective immune cell restraints that cancer cells use to stave off an immune attack.

The approach is part of ongoing research aimed at employing the immune system to attack cancer. “We’re trying to find that optimal balance between pushing and pulling the immune system to kill cancer,” says Charles Drake, M.D., Ph.D., associate professor of oncology, immunology, and urology. In this study, the proteins released by tumor cells when they are killed by radiation are used to bait immune cells, and the immune therapies are used to advance and augment the immune response against the brain cancer.

The researchers also observed a vaccine effect. When brain tumor cells were later reintroduced under the skin of mice, the immune system recognized and attacked the cancer cells. This type of immune memory is an exciting finding because it demonstrates the poten-
tial to engage the immune system to keep cancer at bay indefinitely.

Drake collaborated with Michael Lim, M.D., director of the Johns Hopkins Brain Tumor Immunotherapy Program and Metastatic Brain Tumor Center. Studies to affirm the value of the combined therapy are ongoing, and a number of clinical trials for brain tumors are in development.

The WW Smith Charitable Trust and individual patient donors funded the research. Full disclosure of patents and corporate support are available at hopkinscancer.org.

Test for Oral Cancers
JAMA Otolaryngology, July 9, 2014

Johns Hopkins scientists developed blood and saliva tests to help detect HPV-linked oral cancers that have come back after treatment. The tests detect HPV (human papilloma virus) DNA shed from cancer cells.

“There is a window of opportunity in the year after initial therapy to take an aggressive approach to spotting recurrences and intensively addressing them while they are still highly treatable. Until now, there has been no reliable biological way to identify which patients are at higher risk for recurrence, and these tests will help us do so,” says Joseph Califano, M.D., professor of otolaryngology-head and neck surgery, member of the Kimmel Cancer Center, and medical director of the Milton J. Dance, Jr., Head and Neck Center at Greater Baltimore Medical Center. Current methods of detecting recurrence, including physical examinations and imaging, have not worked well.

In a small study of patients with HPV-positive oral cancers, Califano found that detecting HPV DNA in both blood and saliva was most predictive for cancer recurrence. He is now working to further improve the tests. “We have to be sure that positive test results are cancer-specific and not related to other forms of HPV infection or exposure,” he says.

The research was funded by the National Institutes of Health’s National Cancer Institute/National Institute of Dental and Craniofacial Research (P50 CA19032).

Game Theory and Cancer
Interface Focus, June 20, 2014

Game theory is a mathematical study of strategic decision-making that has been widely used to predict conflict and cooperation among people and nations. Now, prostate cancer scientist Kenneth Pienta, M.D., and Ardeshir Kianercy, Ph.D., a researcher in his lab, are using it to forecast cell-to-cell interactions in cancer.

“Tumors contain a variety of cells shifting between cooperative-like and competitive-like states,” says Kianercy. “To study tumor cells in isolation is not enough. It makes sense to study their behavior and relationship with other cells and how they co-evolve together.”

Pienta and Kianercy used mathematical and computer tools to set up game parameters based on biological interactions between two types of tumor cells to explore how they engage in different types of energy metabolism. Applying their game theory calculations the researchers uncovered critical transitions when a tumor suddenly switches its energy metabolic strategy.

This switch may foretell progression and spread of cancer, says Pienta, the Donald S. Coffey Professor of Urology and director of the Brady Urological Institute’s Prostate Cancer Program. He thinks tumors may be particularly vulnerable during this strategy-switching period, and it could be an ideal time to use clinical interventions to disrupt the cell-to-cell cooperation that permits cancer cell growth and spread. “If cells become non-cooperative, they are most likely to stay in that state, and the tumor may become more vulnerable to anticancer therapies,” says Kianercy.

Pienta isn’t sure if this type of energy metabolic cooperation occurs in all tumors, but the model gives scientists a new way to study how cancers may progress. He says, “The reality is that we still can’t cure cancer that has spread from its primary organ, and game theory adds to our efforts to attack the problem.”

The research was funded by the National Institutes of Health’s National Cancer Institute (U54 CA143803).
AMEN to Miracles
The Journal of Oncology Practice, June 16, 2014

A new tool developed by Kimmel Cancer Center clinicians and chaplain Rhonda Cooper helps doctors, nurses, and other caregivers talk to dying patients and their families who are praying for a miracle. The tool, called AMEN—an acronym for Affirm, Meet, Educate, No matter what—provides a conversational protocol caregivers may use to communicate with patients and families in this situation. Its tenets are: Affirm or acknowledge patients’ hope, meet or join them in their hope, continue to educate the patients and families about medical issues, and assure them that their health care team will remain with them throughout the duration of their care, “no matter what.”

A study cited by Cooper and conducted by the University of Connecticut and Georgetown University finds that the majority of adults—57 percent—randomly surveyed said they believed that “God’s intervention could save a family member” even when physicians said that further treatments would be futile. The team developed the tool because many medical professionals are uncomfortable, even dismissive, of such beliefs, and it can affect the trust between patients and caregivers.

“The tool can remind providers to ask, not assume, what patients in treatment are hoping for,” says Anna Ferguson, R.N., a collaborator on the AMEN tool and director of the center’s Hope Project that, like the AMEN tool, educates caregivers on ways to integrate patients’ hopes into their treatment plan.

“Our goal is to maintain trust and foster open and honest communication as the care plan is being discussed,” says Cooper, “and to help medical experts see the hope for a miracle as an opportunity to join the patient or family in their end-of-life conversation.”

Broccoli Sprouts Detoxify Dirty Air
Cancer Prevention Research, June 9, 2014

A half cup of a broccoli sprout beverage a day could keep carcinogens and irritating pollutants at bay, based on findings from a clinical trial involving nearly 300 Chinese men and women living in one of the country’s most polluted regions. Drinking the sulforaphane-rich beverage produced rapid, significant, and sustained excretion of benzene—a known human carcinogen, and acrolein, a lung irritant.

The participants were from the Jiangsu Province in China, about 50 miles from Shanghai, one of China’s most industrialized regions. They were followed for 12 weeks using urine and blood samples to measure the fate of inhaled pollutants.

Sulforaphane is a natural, plant-based compound found in high concentrations in broccoli sprouts which Johns Hopkins research has shown to have cancer prevention properties. Additional analysis of the Chinese participants revealed that the sulforaphane activated a cancer-protective gene pathway known as NRF2 that helps cells adapt to and survive a broad range of environmental toxins.

“Air pollution is a complex and pervasive public health problem,” says John Groopman, Ph.D., the Anna M. Baetjer Professor of Environmental Health at the Bloomberg School of Public Health. “To address this problem comprehensively, we need to translate our basic science into strategies, like this one, that protect individuals from this exposure.”

The World Health Organization estimates that air pollution causes as many as 7 million deaths worldwide each year. Last year, the International Agency for Research on Cancer classified air pollution and particulate matter (solid and liquid particles in the air, such as soot, dirt, and smoke) from air pollution as human carcinogens.

“This study points to a frugal, simple, and safe means individuals can use to possibly reduce some of the long-term health risks associated with air pollution,” says Thomas Kensler, Ph.D., a school of public health researcher and study co-author. Trials to evaluate optimal dosage and frequency of the broccoli sprouts beverage are ongoing.

The trial was supported by the National Institutes of Health (P01 ES006052 and P30 S003819) and Safeway Inc.

Only on the Web
http://magazine.jhsph.edu/2014/fall/features/one-fresh-cancer-prevention
World’s First Protein Catalog

Nature, May 29, 2014

An international team of researchers created a catalog of all of the proteins in the human body. The project was led by researchers at The Johns Hopkins University and the Institute of Bioinformatics in Bangalore, India. It is expected to be an important resource for biological research and medical diagnostics.

“You can think of the human body as a huge library where each protein is a book,” says Akhilesh Pandey, M.D., Ph.D., a member of the McKusick-Nathans Institute of Genetic Medicine and the Kimmel Cancer Center. “The difficulty is that we don’t have a comprehensive catalog that gives us the titles of the available books and where to find them. We think we now have a good first draft of that catalog.”

So far, Pandey and team used 30 different human tissues to catalog proteins encoded by 17,294 genes, which is about 84 percent of all of the human genes predicted to encode proteins. Among them were 193 novel proteins from unexpected regions of the genome thought not to code for proteins. This finding suggests that the human genome is more complex than previously thought. “The fact that 193 of the proteins came from DNA sequences predicted to be noncoding means that we don’t fully understand how cells read DNA, because clearly those sequences do code for proteins,” says Pandey.

Pandey says the complex and diverse structure and function of proteins makes their study far more technically challenging than the study of genes. Therefore, most protein studies to date have not been comprehensive and were done in the context of specific diseases.

“By generating a comprehensive human protein dataset, we have made it easier for other researchers to identify the proteins in their experiments,” says Pandey. “We believe our data will become the gold standard in the field.” He says that the human proteome is so extensive and complex that the catalog will likely never be fully complete, but this work provides a solid foundation for others to build upon.

The research was funded by the National Institute of General Medical Sciences (U54 GM103520, P41 GM103504), the National Cancer Institute (U24 CA160036), the National Heart, Lung and Blood Institute (HHSN268201000032C), the Sol Goldman Pancreatic Cancer Research Center, India’s Council of Scientific and Industrial Research, and Wellcome Trust/DBT India Alliance.

Human Chemical Detoxifiers

Food and Chemical Toxicology, May 19, 2014

A compound in saliva and proteins in blood and muscle may protect human cells from powerful toxins, known as polyphenols, found in tea, coffee, and liquid smoke flavoring.

Research led by Kimmel Cancer Center investigator Scott Kern, M.D., the Kovler Professor of Oncology and Pathology, suggests a natural defense against DNA-damaging chemicals found in commonly consumed beverages and flavorings. In laboratory research, Kern and team, observed DNA damage caused by the toxins was far more extensive that caused by chemotherapy drugs, so they knew that cells must be fighting back.

“These chemicals are in the foods and drinks people consume everyday, and they damage DNA to such a high degree that there should be far more illness from them,” says Kern. “We wanted to find the mechanisms that protect us on a daily basis from the plants we choose to eat.”

His research revealed an enzyme in saliva called alpha-amylase, the blood protein albumin, and muscle protein myoglobin as the cell defenders. In addition, they found that cells repeatedly exposed to the toxins appeared to develop resistance to them and no longer required the help of the enzymes and proteins,
perhaps proving the adage, Kern says, “What doesn’t kill us makes us stronger.”

Kern hopes his research will reveal how these natural defenses are circumvented in some people, causing cancer and other illnesses.

_The research was funded by the National Institutes of Health (CA63924) and the Everett and Marjorie Kooler Professorship in Pancreas Cancer Research._

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**Tiny “Ship” Delivers Death Command to Brain Cancer**

*ACS Nano, April 26 and March 27, 2014.*

Researchers used tiny biodegradable nanoparticles to deliver “death genes” to human brain cancer cells implanted in mice. Johns Hopkins biomedical engineers collaborated with neurosurgeons to use the nanoparticles to transport and turn on a test gene in the animal model. The team says the results are proof-of-principle that one day such particles could be loaded with a gene and given to brain cancer patients during neurosurgery to selectively kill off any remaining tumor cells without harming normal brain tissue.

Green worked with neurosurgeon Alfredo Quinones-Hinojosa, M.D., and used glioblastoma brain cancer cells donated by Quinones-Hinojosa’s patients to develop the nanoparticle vehicle that is able to deliver tumor-destroying DNA instructions directly to cancer cells. Green specializes in producing the tiny, round biodegradable plastic particles and tested dozens of variations to find the best one for transporting the gene instructions.

For the test voyage of the nanoparticle, the cargo was a gene that causes cells to glow red or green. Although the nanoparticles entered healthy cells and cancer cells in similar numbers, healthy cells rarely produced the glowing protein. “This is exactly what we wanted to see—cancer specificity,” says Green, “but we are still researching the mechanism that allows this to occur.”

In a related animal study, Green used a different particle to effectively carry and deliver another cancer fighting cargo. This particle delivered siRNAs—interfering molecules that can turn cancer genes off.

Brain cancers are among the most lethal types of cancer with few curative treatment options. “It is exciting that we have a found a way to safely and selectively target genetic instructions to cancer cells,” says Quinones.

_The research was funded by the National Institute of Biomedical Imaging and Bioengineering (IR01 EB016721), the National Cancer Institute (R21 CA152473, R25 CA153952), and the Maryland Stem Cell Research Fund-TEDCO._

**Watch a video**

http://youtu.be/HauXIIDQ36Q

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**No More Repeat Prostate Biopsies**

*Journal of Urology*

A multicenter team of researchers reported that a commercial test for the presence of genetic biomarkers of prostate cancer may be accurate enough to exclude the need for repeat biopsies in most men.

The test is based on the GSTPi gene, discovered by Kimmel Cancer Center Director William Nelson and linked specifically to prostate cancer. GSTP-1 is not found in any normal cell. The commercialized urine test screens for the biomarker and is most useful for men who are suspected to have prostate cancer because of an abnormal exam or rising PSA (prostate specific antigen) levels, despite a negative biopsy.

Prostate biopsies miss about 20 percent of cancers, and the test helps address this uncertainty. If results are negative, it confirms the original biopsy results and could be used instead of repeated biopsies to rule out the presence of cancer.

Results of this most recent research, called the Detection of Cancer Using Methylated Events in Negative Tissue (DOCUMENT) study, suggest that an initial biopsy complemented with the GSTPi biomarker test accurately rules out the existence of cancer up to 88 percent of the time.

“Our research finds that by looking for the presence or absence of cancer in a different way, we may be able to offer many men peace of mind without putting them through the pain, bleeding, and risk of infection that can come with repeat biopsy,” says Jonathan Epstein, M.D., director of the Division of Surgical Pathology, and professor of pathology, urology, and oncology. “The test isn’t a 100 percent assurance, but it is a major step forward,” says Epstein, who is also the Rose-Lee and Keith Reinhard Professor of Urologic Pathology.

MDxHealth developed the commercial test and funded the study.
Philanthropy

Theodore DeWeese Named Inaugural Kimmel Professor

Businessman and philanthropist Sidney Kimmel visited the Kimmel Cancer Center on Nov. 6, 2014, to participate in the dedication of the Kimmel Professor of Radiation Oncology and Molecular Radiation Sciences. Theodore DeWeese was named the inaugural recipient.

The gift to establish the professorship is the most recent in a series of donations to the Cancer Center, which began with his historic $150 million gift in 2001 that led to the naming of the Center in his honor.

“Your generosity continues to amaze and inspire. With Kimmel Scholars putting their mark on cancer research, great institutions like ours that you have supported, and now this incredible professorship, your philanthropy is what makes cancer a curable disease,” said Kimmel Cancer Center Director William Nelson. He called Kimmel’s continuing support an instrument for stability.

Endowed professorships are critically important to the ongoing mission of Johns Hopkins University as they provide lasting support for the most talented faculty members. They are recognized as the university’s highest honor to its faculty. “The importance of an endowed professorship cannot be overstated,” says Nelson. “It is often the critical element in helping us have the very best people come here and succeed here.”

The formal dedication of the professorship included a presentation by Paul Rothman, dean of the medical faculty
and CEO of Johns Hopkins Medicine, to Johns Hopkins University President Ronald Daniels. Rothman told the audience of more than 100 faculty, staff, and invited guests, that Kimmel’s generosity had allowed Cancer Center experts to push the boundaries of science. “Having been at Johns Hopkins for just two years, I can speak from the perspective of being outside the institution and inside,” said Rothman. “The Kimmel Cancer Center is unquestionably one of the leading institutions in the world helping to prevent and cure cancer.”

In accepting the professorship on behalf of the university, President Daniels said Kimmel’s contributions have transformed the fight against cancer. Kimmel is one of a very small group of American philanthropists who have turned over more than half of their wealth to charitable causes. Of the more than $850 million he has donated, most—some $550 million—has gone to cancer research.

DeWeese, who in 2003 was selected as the first director of the Department of Radiation Oncology and Molecular Radiation Sciences, was named the inaugural Kimmel Professor in recognition of his many research, clinical, and teaching accomplishments. Under his guidance, the department has earned a reputation as one of the very best in the world.

“As a researcher, clinician, and academician, Ted has championed interdisciplinary research that has truly transformed his discipline,” says Daniels. “His efforts have kept our department strong and ensured it has remained at the forefront of innovation.”

“Ted has had an incredible career. I have great pride in having someone with such enormous skill and deep compassion be the first to hold the professorship bearing my name,” says Kimmel. “This is an honor I could have never imagined growing up as poor kid in South Philadelphia. Coming back to Johns Hopkins each time is rejuvenating for me. The work done here and the results achieved leave me in awe.”

After being installed as the inaugural Kimmel Professor, DeWeese recognized the faculty and staff of his department and thanked Kimmel. “Many people beyond me have played a role in earning this honor. Whatever success I have had is shared by the talented faculty and staff in our department,” he said.

“The gifts Mr. Kimmel has given in support of cancer care and research, the programs he has started, and the trainees he has supported are innumerable. Yet the nature of his giving is that they all have direct relationship to patients,” said DeWeese. “To have my name forever linked with his is humbling. His contributions are given with hope and the recognition that some patient, somewhere, someday, is going to benefit. Because of him, cancer research will be improved and advanced, suffering will be relieved, and ultimately a cure will be found.”

The Kimmel Scholar
During his visit, Mr. Kimmel had the opportunity to meet with a 2014 Kimmel Scholar, Andrew Holland, a young researcher who has developed a mouse model to study cell division and how it goes awry in cancer.

Holland says the process of cell division occurs millions of times in our bodies each day as old cells are replaced by new cells. Errors in cell division are one of the hallmarks of cancer. Holland is using the mouse model to mimic these errors and study how they contribute to cancer development and growth. He hopes to decipher ways to specifically destroy cells undergoing abnormal cell division while leaving normal cells unharmed.

“I feel privileged to have received this award,” says Holland. “The resources that the Kimmel Scholar foundation provides are benefitting the whole lab and allowing us to pursue risky, but important research that has the promise to have a real impact on human disease.”

Watch a movie of dividing cancer cells at hopkinscancer.org

IN NORMAL CELL DIVISION, DNA IS EQUALLY PARTITIONED INTO THE TWO NEW CELLS. IN THE DIVISIONS OF CANCER CELLS, DNA IS OFTEN MISPLACED. THE 2014 KIMMEL SCHOLAR ANDREW HOLLAND BELIEVES THIS TYPE OF MISTAKE IN CELL DIVISION ALLOWS CELLS TO SHUFFLE THEIR CHROMOSOMES AND ACQUIRE NEW GENETIC INFORMATION THAT ALLOWS THE CELL TO BEHAVE ABNORMALLY, SELECTING FOR GENETIC INSTRUCTIONS THAT PROVIDE GROWTH-PROMOTING PROPERTIES.
Sustaining a 20-Year Partnership
Komen Maryland and Johns Hopkins

THROUGHOUT THE ONGOING 20-year partnership between Susan G. Komen®, the Maryland Affiliate, and Johns Hopkins, tremendous strides have been made against breast cancer. “We are so fortunate to have a Komen affiliate and partner in Baltimore. It has touched everything we do in breast cancer,” says William Nelson, M.D., Ph.D., Director of the Johns Hopkins Kimmel Cancer Center. “From investing in our young people and our most experienced scientists, to removing barriers to screening for the most vulnerable of our state, helping move new treatments to the clinic, and most recently providing funding for survivorship, Johns Hopkins and Susan G. Komen have focused on many breast cancer issues together.”

Through coordination with the Susan G. Komen National Research, Evaluation, and Scientific Programs, Komen Maryland has supported the work of breast cancer scientists and clinicians and played a major role in charting the course of progress against the disease.

With an investment of nearly $1.4 million since the partnership began in 1994, and under the direction of CEO Robin Prothro, Komen Maryland has addressed and influenced many important issues related to breast cancer. In 2001, as the founding director, Ms. Prothro grew the Maryland affiliate from a grassroots, all-volunteer organization to a recognized force in breast cancer advocacy and change. She and her team have navigated screening participation, recommendation and reimbursement controversies, and racial disparities and access to care barriers. They have influenced important issues such as the development of targeted therapies and the resulting long-term survivorship and evolution of breast cancer into a chronic disease.

We recently had the opportunity to chat with Ms. Prothro about these achievements.

Q. As you reflect on the accomplishments of the last 20 years, what comes to mind?
A. I feel like we have come full circle. Originally, as an advocacy organization, we worked to get the word out about breast cancer screening and early detection and ensuring that everyone has access to these services. Then we moved to therapy, working for better accrual to clinical trials, which led to improved treatments. The benefits of this work are now being realized in the form of survivorship. Women are surviving breast cancer in record numbers because they are getting screened, and therapy has dramatically improved as a direct result of Susan G. Komen-supported research.

Q. As you noted, breast cancer survivorship has increased significantly. Specifically, how has Komen Maryland helped influence this trend?
A. Early detection is key to surviving cancer. Komen Maryland local grants targeted minority communities, providing education about breast cancer prevention and detection, and facilitating mammography, treatment, and support. Susan G. Komen was a force in raising awareness about breast cancer, ensuring women access to screening, and tackling reimbursement issues to make breast cancer prevention and screening standard of care.
Komen Maryland, by the Numbers

- **48,000** people reached
- **21,000** people educated about breast cancer and breast health
- **8,453** women received free clinical breast exams
- **6,775** women received free mammograms
- **5,822** people of underserved populations, including African American, Hispanic, Asian, and other ethnic women received free mammograms
- **3,705** survivors and families received counseling and other support services
- **2,108** people educated, screened, and enrolled in clinical trials
- **256** women enrolled in clinical trials
- **131** minority women enrolled in clinical trials
- **61** breast cancers were diagnosed
- **51** men received diagnostic and other support services

Q. Komen Maryland has been a key supporter of clinical trials, funding more trials than any other Komen affiliate. What drove this focus and how has it made a difference?  
A. With increased breast cancer screening participation and racial and ethnic disparities highlighted, Komen Maryland began a sustained effort of supporting patient accrual to clinical trials. This effort advanced care, and ensured that breast cancer patients had access to state-of-the-art therapies. These trials played a key role in bringing about technical advances, such as lumpectomy and sentinel node biopsy, as well as a new understanding about the unique biology of breast cancer—illuminating which treatments worked for which cancers and which ones did not. Breast cancer became the model for targeted therapies, and these advances are now being applied to other cancers.

Q. Cancer survivors are the most rapidly growing demographic, and many of them are breast cancer survivors. From 1994 to 2004, the number of women living with breast cancer increased by nearly 30 percent. What is Komen Maryland doing to support this growing segment of the population?  
A. The impact of early detection and advances in treatment are now being realized in long-term survivorship. Breast cancer is being transformed into a survivable, chronic disease, and Komen Maryland is working to ensure that women live longer and live well. Survivorship has become a specialized area of medicine, and we are working with breast cancer and survivorship experts at the Kimmel Cancer Center to create the model for best practices and standard of care for breast cancer survivors. Grants to Johns Hopkins have advanced the study of survivorship, funded survivorship retreats for patients and caregivers, psychosocial assessments, complimentary and alternative care such as acupuncture, and coordination of care and transition to survivorship care. Susan G. Komen has spent almost $90 million researching metastatic disease looking for better detection and treatment to minimize the effects this disease can have on one’s life.

Q. Any predictions for the next 20 years?  
A. Innovations, discoveries, and technologies have catapulted expectations. We are on the frontier of great advances, and we must maintain this pace and energy to overcome current hurdles in breast cancer diagnosis, treatment and care. Given the innovations and cancer gene discoveries of the last ten years, we expect that the next 20 years will see more and better targeted therapies, a greater ability to diagnose at earlier stages, and more sophisticated and applied personalized medicine to prevent cancer. Over the next 20 years, we need to sustain our efforts to achieve our goal of eliminating breast cancer.
The Ride to Conquer Cancer
September 2014 marked the Capital Region’s inaugural Ride to Conquer Cancer. The starting lineup included more than 1,000 participants eager to take on the scenic 150-mile course. Each rider raised a minimum of $2,500. Together, they raised $2.6 million for the Johns Hopkins Kimmel Cancer Center, Sibley Memorial Hospital, and Suburban Hospitals, where the funds are already being used to support lifesaving cancer research and accelerate transformational cancer discoveries.

Planning has already begun for next year’s event, scheduled for Sept. 19 and 20, 2015.

Register to ride at ridetovictory.org.

Swim Across America
The fifth annual Swim Across America (SAA) Baltimore event raised $480,000 for the Kimmel Cancer Center’s Swim Across America Laboratory. On Sept. 20 and 21, 2014, more than 600 swimmers participated in a pool swim at Meadowbrook Aquatic and Fitness Center and an open-water swim at High Tide Farm on the Magothy River.

Festivities also included appearances by several Olympic swimmers, including Patrick Kennedy (’84), Theresa Andrews (’84), Brenda Borgh Bartlett (’76), Tara Kirk Sell (’04), and Swim Across America’s president and CEO, Janel Jorgensen Mc Ardle (’88), who visited pediatric cancer patients. SAA-funded investigator Dung Le, M.D., reported on advances being made through clinical trials supported by the Swim Across America Laboratory.

In total, SAA swimmers have raised over $2 million for cancer research. Funding supports basic research that can be translated for the development of new diagnostic and treatment approaches for patients with cancers.

The Swim Across America Laboratory is directed by cancer genetics expert Luis Diaz, M.D. Among his research advances are the PapGene test study, which holds promise in facilitating the early detection of ovarian and endometrial cancers, and personalized biomarkers that use cancer DNA to better screen for and monitor cancers.

Only on the Web: Inside the Swim Across America Research Lab at Johns Hopkins http://bit.ly/1rw8pFI
In The News

New Appointments

Satish Shanbhag, M.B.B.S., M.P.H., is the new medical director of Johns Hopkins Bayview Medical Center's oncology/hematology outpatient practice. His leadership will include collaborations with leaders in upper aerodigestive diseases, radiation oncology, pulmonary medicine, and thoracic surgery to foster a patient-centered, safe, efficient and evidence-based environment.

Sara Sukumar, Ph.D., has been appointed assistant director for faculty affairs. She will chair the department of oncology’s Appointments, Promotions, and Career Development Committee, which oversees the selection of individuals for appointment to the faculty and for promotion.

New Faculty

Lukasz Gongdek, M.D., Ph.D., instructor in oncology, joined the hematologic malignancies program. Gongdek is a physician-scientist with a strong background in both basic-translational research and medicine, with a particular interest in the biology of myelodysplasia. He has pioneered many of the seminal findings in the field of myelodysplastic syndrome (MDS) and leukemia genetics. He plans to develop a laboratory-based translational research program focused on MDS stem cell biology and targeted therapies in myelodysplasia and will work closely with members of the adult clinical leukemia service to translate his findings to the clinic.

Jeffrey S. Huo, M.D., Ph.D., has joined the Pediatric Oncology Program as an instructor of oncology and pediatrics. Huo’s research is focused on the relationship between cancer epigenetic reprogramming in stem cells. He is developing a stem cell model of human retinoblastoma. Huo is a Maryland Stem Cell Research Fund postdoctoral fellow and Alex’s Lemonade Stand Young Investigator. Huo was a magna cum laude graduate of Northwestern University’s honors program in medical education. He received his medical degree and doctorate in cellular and molecular biology through the University of Michigan’s medical scientist training program.

Nicolas J. Llosa, M.D., instructor of pediatrics and oncology, is a new member of the Pediatric Oncology Program. His research focuses on understanding immune checkpoint expression in the tumor microenvironment in sarcomas and other cancers, and using his findings to identify potential biomarkers for immunotherapeutic interventions that involve checkpoint blockade. Llosa received his medical degree from the National University of Cuyo in Argentina and completed a fellowship in medical research at the Brigham and Women’s Hospital in Boston. He was chief pediatrics resident at Tufts. He served as chief fellow in the Johns Hopkins/National Cancer Institute joint pediatric hematology and oncology fellowship program.

Allison Martin, M.D., has joined the Pediatric Oncology Program as an instructor in pediatrics and oncology. She is researching immune therapy strategies, including the immune blockade target PD-L1, in pediatric brain tumors with the aim of developing a phase I clinical trial of anti-PD-1 therapy in pediatric brain tumors. Martin received her medical degree from Jefferson Medical College.

Christine Pratilas, M.D., assistant professor of oncology and pediatrics, was selected after an international search to join the Pediatric Oncology Program. Pratilas will specialize in pediatric sarcomas and other solid tumors. She comes to the Kimmel Cancer Center from Memorial Sloan Kettering Cancer Center where she was a faculty member for eight years.

Ravi Varadhah, Ph.D., has joined the Biostatistics and Bioinformatics Division as an associate professor of oncology in the Division of Biostatistics and Bioinformatics. He also holds joint appointments at the Johns Hopkins Center on Aging and Health and Department of Biostatistics and at the Bloomberg School of Public Health Center for Drug Safety and Effectiveness. Ravi is a highly-trained mathematical modeler with doctorates in environmental engineering and biostatistics. He is a co-director for the Biostatistics and Epidemiology of Aging Training Program at Johns Hopkins and has published numerous articles in engineering, environmental science, applied mathematics, statistics, epidemiology, gerontology, and biomedical journals.
Honors and Awards

Nurse Executives
The Kimmel Cancer Center was the site of the biannual meeting of the National Cancer Institute-designated comprehensive cancer centers’ nurse executives. The two-day meeting was hosted by Sharon Krumm, Ph.D., R.N., director of nursing and clinical administrator, and addressed a variety of topics, including survivorship, symptom management, and radiation treatment for pediatric patients.

Friends of Oncology
Congratulations to those who were honored by Friends of Oncology with nursing clinical excellence, advanced practice, research nurse, and clinical technician awards for excellence in providing comprehensive and compassionate care to patients and families:
Lynn Billings, B.S.N., R.N., CHPN, BC
Katie Boyle, M.S.N., R.N.
Christopher Dillman
Haley Gibbs, Pharm.D., BCPS
Nicole Herman, B.S.N., R.N.
Amy Horne, B.S.N., R.N., OCN
Nikkya Johnson-Brooks
Nikkya Johnson-Brooks
Ella Mae Shupe, R.N.
Marie Swisher, M.S.N., R.N., CWCN, AOCNS
Ann Toland
Bridget Trias, R.N., OCN
Karla Maria Viloria, B.S.N., R.N.
Betsy Zink, M.S., R.N., C.C.N.S., C.N.R.N

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READ ABOUT DR. TED DEWEES’S EVEREST ADVENTURE

WWW.HOPKINS CANCER.ORG
Deborah Armstrong, M.D., was appointed chairperson of the Food and Drug Administration’s Oncologic Drugs Advisory Committee.

Ross Donehower, M.D., was inducted into the Miller-Coulson Academy of Clinical Excellence, an initiative sponsored by the Center for Innovative Medicine to recognize masterful physicians who are steadfastly committed to clinical excellence for the benefit of the patients and communities that they serve.

Patrick Forde, M.B.B.Ch., received a LUNGevity Foundation Career Development Award for his project titled “Neoadjuvant anti-PD-1 antibody, Nivolumab, in resectable nonsmall cell lung cancer NSCLC.” The foundation supports “the nation’s future research leaders who keep the lung cancer field vibrant with new ideas.”

Gregory Kirk, M.D., Ph.D., M.P.H., was awarded a National Cancer Institute (NCI) Grant for Global Health. The grants promote research collaborations among NCI-designated cancer centers and institutions in low and mid-income countries. Kirk will collaborate with Posiano Ocampo, from Makerere University in Uganda, on HIV infection, viral hepatitis and liver cancer research in Uganda. Johns Hopkins was one of only 15 institutions to receive an award.

Louise Knight, director of the Harry J. Duffey Family Patient and Family Services Program, was selected for the Medicare and Medicaid Advisory Panel on Outreach and Education. The panel advises the Secretary of Health and Human Services and the administrator of the Center for Medicare & Medicaid Services on the effective implementation of the Medicare, Medicaid and the Children’s Health Insurance Program. A growing focus of the panel is on Affordable Care Act enrollment among vulnerable and underserved communities in the exchanges and the expanded Medicaid program.

Marikki Laiho, M.D., Director of our Molecular Radiation Sciences Division, received a 2015 Harrington Scholar-Innovator Award. The highly competitive award recognizes physician-scientist innovators throughout the U.S. whose research has the potential to change standard of care.

Clinical nurse specialist Mikaela Olsen, R.N., M.S., received an honorable mention by the Medical Book Awards as co-author for the book Hematologic Malignancies in Adults.

The Melanoma Research Alliance gave its Team Science Award to Bert Vogelstein, M.D.; Drew Pardoll, M.D., Ph.D.; and Evan Lipson, M.D. The three-year grant will be used to develop new therapeutic approaches and improve existing treatments. Projects will include the identification of biomarkers that predict response to therapy and studies of multi-drug combinations.

Bert Vogelstein, M.D., was one of three inaugural recipients of the $5 million Lustgarten Foundation Distinguished Scholars award. The foundation is the largest private foundation in the U.S. dedicated to funding pancreatic cancer research.

The HERA Women’s Cancer Foundation, a nationally recognized ovarian cancer nonprofit, awarded its Outside the Box grants to Lingling Xian, M.D., Ph.D.; Blanca Valle, M.D., Ph.D.; and Christian Schuetz, Ph.D., to pursue novel ways to detect and treat ovarian cancer. The investigators plan to study personalized targeted stem cell therapies, biomarkers for early detection, and immune therapies.

Pediatric Oncology Awards:

The St. Baldrick’s Foundation announced funding for six of our pediatric oncologists: Sama Ahsan, M.D., received a Young Investigator Grant to study the epigenome of brain stem glioma, a difficult-to-treat form of pediatric brain cancer. Colleen Annesley, M.D., received the Tap Cancer Out St. Baldrick’s Fellow award for her research on specific mutations that could lead to new targeted therapies for acute myeloid leukemia. Christopher Gamber, M.D., Ph.D., received the St. Baldrick Scholar award, with support from the McKenna Claire Foundation, to study immune therapies and strategies to reduce late effects of chemotherapy and radiation therapy. Jeffrey Huo, M.D., Ph.D., was awarded a Young Investigator Grant to characterize the epigenetic origins of the retinoblastoma tumor-initiating cell. Jeffrey Lukish, M.D., received a supportive research grant for research aimed at preserving fertility in pediatric cancer patients. Eric Raabe, M.D., Ph.D., received the Heroes for Hannah Award for his research to develop better models of high-risk medulloblastoma brain cancer to test new therapies.

Alex’s Lemonade Stand Foundation awarded Innovation Grants to Alan Friedman, M.D., and Linda Resar, M.D. Friedman will use his funding for research on glioblastoma multiforme brain cancer and ways to recruit normal cells to hold it in check. Resar will study the genetic causes of relapse and resistance in acute lymphoblastic leukemia. Friedman and Resar were the only pediatric oncologists in Maryland awarded Innovation Grants.

Josh Lauring, M.D., Ph.D., follows Elana Fertig, Ph.D., as the recipient of the Cleveland Foundation Internal Junior Faculty Award.
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