PROMISE & PROGRESS

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

A Look Inside Our Cancer Medicine Cabinet

One-of-a-Kind Advances in Drug Discovery and Development

P&P

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Driving Drug Discovery

DRUG DISCOVERY is complicated, difficult work, but Kimmel Cancer Center experts are among the best at it, a distinction they have held for nearly four decades. In 1979, our cancer center was one of the first to earn a National Cancer Institute grant for new drug development, and today we remain one of the select few to maintain this support. From early work with cyclophosphamide to today's breakthrough immunotherapies, our experts have a proven track record of success in translating laboratory and clinical discoveries into new cancer medicines for patients.

To ensure these advances continue in a new research environment, where the onus of early drug discovery and development has shifted from the pharmaceutical industry to the academic researcher, we are working to bring a reimagined drug discovery and development engine to the Kimmel Cancer Center.

Despite its difficulty, drug discovery thrives in our unique environment of collaboration and unparalleled expertise in virtually every area of bench-to-bedside cancer research. Discoveries in these fields are providing the cancer targets that are driving new drug development and precision medicine.

Our experts are identifying cancer-promoting molecular targets, inventing drugs that go after them and developing tests that can identify patients who have cancers with the targeted defect. As a result, clinical trials are being designed to test new drugs only in the patients they are most likely to help—those whose cancers contain the defect that will respond to the drug. This allows clinical trials to progress more rapidly and new drugs to get approved faster and at a much lower cost.

As we near completion of the 10-story Skip Viragh Outpatient Cancer Building, we are poised to provide and move forward the most advanced and sophisticated cancer care. Our depth of expertise in cancer research and drug discovery, and the most technologically advanced and patient-centered clinical facilities set the Kimmel Cancer Center apart as among the most talent rich and resource ready to develop and study new cancer drugs.

We are committed to providing the necessary drug development tools, resources and funding for our scientists and doctors, and more rapid access to new cancer drugs for our patients.

William G. Nelson, M.D., Ph.D.
Marion I. Knott Professor and Director
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Moving Cancer Medicines Forward

Reimagining drug discovery and development

From scientific meetings to our own dinner tables, conversations about better treatments for cancer are among the most frequently discussed health care topics. Everyone wants them—the doctors and scientists who treat and research cancer, those of us who worry we may one day hear the words "you have cancer," and most certainly the hundreds of thousands who have already been diagnosed. Whether it's old-school chemotherapy or a brand-new immunotherapy, when we say "new treatment," the form this much-sought progress usually takes is a drug—either a new one made from the ground up or an existing one that scientists modify to attack cancer cells.

Much has changed since the early days of developing cancer drugs. Pharmaceutical companies have largely pulled out of drug discovery, leaving academic cancer researchers with the charge to bring cancer medicines forward.

To answer the challenge, Kimmel Cancer Center Director **William Nelson** is restructuring research programs to provide Cancer Center investigators with the laboratory resources they need to maintain their leading edge, fostering collaborations and partnerships to get drugs made and moved ahead. Ultimately, he envisions a reconfigured drug discovery program to garner the scientific and financial resources needed to reduce the time from discovery to clinical trial. "So much time is lost when investigators have to hunt for money to move drug discoveries to the clinic," says Nelson. "We have the expertise to provide the specialized research support and expertise to get promising medicines to patients faster."

Delays in funding are one of the biggest challenges for drug discovery and development. The biggest funding gap comes at the most critical time, just about the time a drug discovery is ready to go to patients. It takes about $2 million to $3 million to make this leap, and this is where many promising projects die. "Our investigators can lose a year or two searching for funding to move forward," says Nelson.

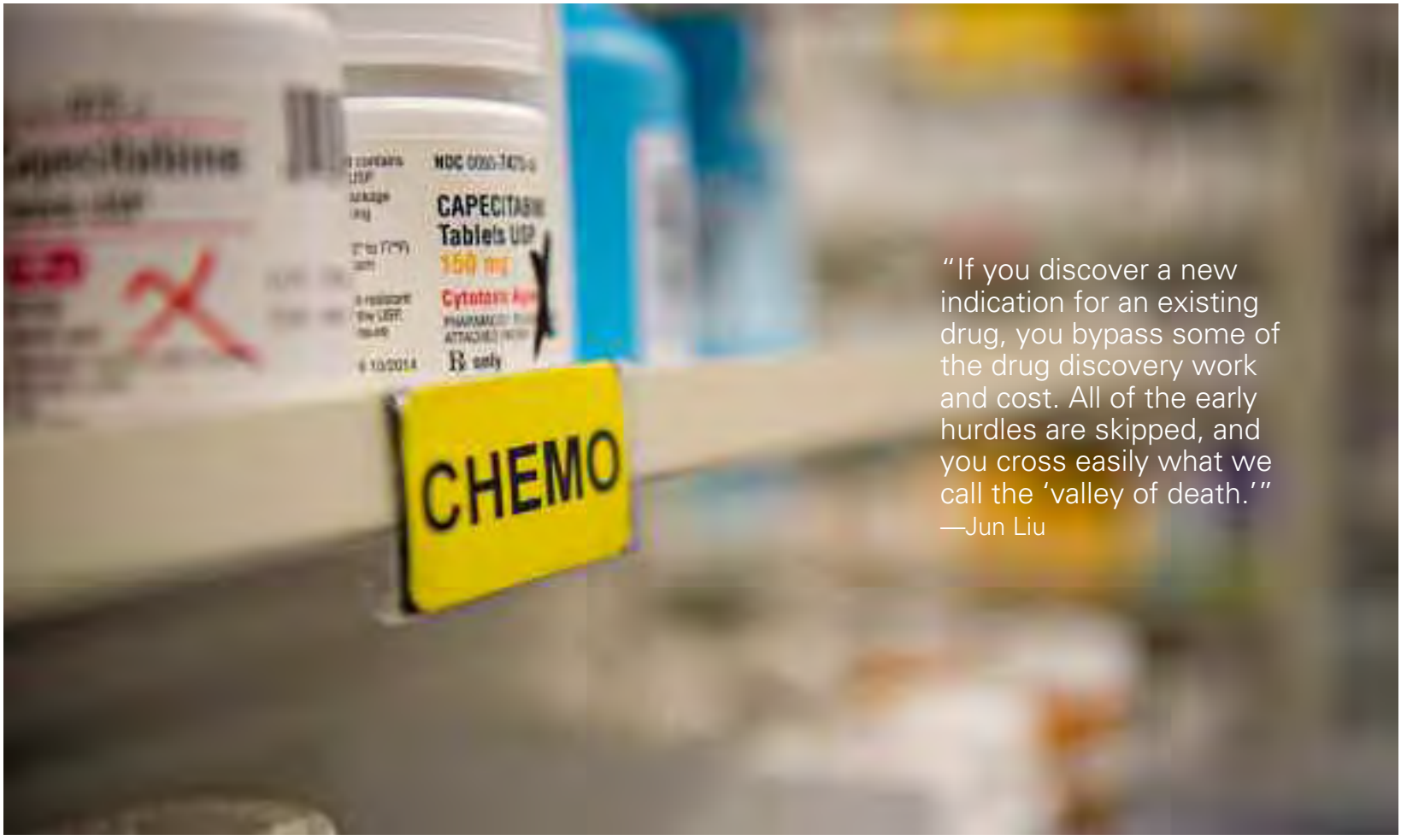
No one understands this better than **James Berger** and **Jun Liu**, who are at the epicenter of drug development for the Kimmel Cancer Center. Liu, a medicinal chemist, and Berger, a biophysicist, lead the Chemical and Structural Biology Program. They are experts in deciphering how drugs travel through the body, where they go, how long they stay there, and how they change the behavior of cells and genes along the way.

"Drug discovery and development are hard and expensive, but if we don't do it, it's not going to get done because pharma has divested itself of it," says Berger, a member of the prestigious National Academy of Sciences. Nelson believes the Kimmel Cancer Center can help shift the curve in a more positive direction through better research models and expert help along the way.

"We have deep expertise in biological cancer targets. We have people who have worked on a target for 20 years and may have even discovered it," says Berger. "They understand its potential and drawbacks better than anyone. If we give these people a little support, it won't take much to figure out if it will work."

Finding new uses for old drugs is one approach that offers both cost savings and a faster route to the clinic. Liu helps researchers search for new uses of existing drugs from a large collections of known drugs called drug libraries. Libraries of FDA-approved drugs used to treat other diseases, catalogs of drugs abandoned by pharmaceutical companies,

JAMES BERGER AND JUN LIU LEAD THE CHEMICAL AND STRUCTURAL BIOLOGY PROGRAM. THEY ARE EXPERTS IN DECIPHERING HOW DRUGS TRAVEL THROUGH THE BODY, WHERE THEY GO, HOW LONG THEY STAY THERE, AND HOW THEY CHANGES THE BEHAVIOR OF CELLS AND GENES THEY COMES IN CONTACT WITH.



"If you discover a new indication for an existing drug, you bypass some of the drug discovery work and cost. All of the early hurdles are skipped, and you cross easily what we call the 'valley of death.'"
—Jun Liu

and libraries of biologics or natural drugs that target and block the communication of specific disease-driving genes provide fertile terrain for scientists hoping to mine for existing drugs they can potentially repurpose as cancer-targeted therapies.

Over the last decade, Liu has cataloged a collection of known drugs that could potentially find a new application in cancer. With more funding, he and his team have plans to grow its scope and size. To be most useful, drug libraries must be continually updated to stay current as new drugs hit the market.

"A drug that is very well-characterized may have some activity against other targets, including cancer targets," says Liu. Clinical trials of known, FDA-approved drugs can advance more quickly because side effects and dosing have already been studied.

Liu is building new molecular libraries that have promise to become cancer drugs. He has already successfully traversed the landscape in his own research, applying a drug library find to cancer and moving it to clinical trials and, ultimately, commercial licensing.

"If you discover a new indication for an existing drug, you bypass some of the drug discovery work and cost," says Liu. "All of the early hurdles are skipped, and you cross easily what we call the 'valley of death.'"

This metaphorical place is very real to investigators who uncover promising cancer targets and drugs, only to see their ideas languish and fizzle out because they are unable to secure funding. The symbolic terminology genuinely reflects a critical crossroads that connects laboratory research to its translation into clinical trials of promising new treatments.

Liu's drug library approach is not a slam dunk. Drugs typically require chemical changes to create a cancer-specific formulation. "Drugs have to be stable and have to be absorbed and accumulated at a certain concentration in humans," says Liu. "They can't just kill cancer cells in a test tube in someone's laboratory. We must be able to give it to humans, if it is going to become a new cancer medicine."

This is familiar work to Cancer Center clinicians and investigators. Paclitaxel is now a mainstay in the treatment of a variety of cancers, but when the drug was first developed decades ago, it was nearly abandoned in the transition from bench to bedside because patients could not absorb the drug into their bloodstream where it could circulate and kill cancer cells. The Kimmel Cancer Center's **Ross Donehower** was among the team that developed premedications that allowed paclitaxel to be safely given to cancer patients. In the late 1980s, the Cancer Center became the first in the nation to report promising results in clinical trials of the drug to treat ovarian cancer, but paclitaxel—acclaimed at the time as the most promising new anticancer drug in 15 years—might never have reached patients if not for the persistence of Donehower and team.

"Academic research brings a lot of people working in a lot of systems to the drug discovery arena. That gives us the ability to generate many fresh ideas and take a lot of shots on goal. We don't expect all of them to pan out."—James Berger

Today, Liu is doing similar work with an anti-fungal drug called itraconazole, which is used to treat toenail fungal infections. In 2006, Liu found the drug among a library of 3,000 FDA-approved drugs. He selected it for its ability to stop two cancer-promoting processes—one known as angiogenesis, where tumors develop blood vessels to get the nourishment they need to grow and spread, and the other, a cancer-initiating biological pathway called Hedgehog.

"We were amazed to find a single drug with multiple anticancer properties," says Liu.

In animal studies, he found the drug was particularly effective against prostate cancer cells. Since the drug was already FDA approved, Liu was able to work with Kimmel Cancer Center prostate cancer experts to move the drug into clinical trials in less than five years.

Liu continues to study how the drug works at the molecular level, and has developed new chemical formulations to address liver toxicities and apply the therapy to other types of cancer.

His most recent research uses the drug as a much-needed treatment alternative for people with basal cell skin cancers. "This cancer is a lifetime threat for patients who have it. They get many tumors on various parts of their bodies, and when the tumors grow to a certain size, they have to be removed with surgery," says Liu. Until his itraconazole discovery, there were limited treatment options for this cancer. Cancers that occurred on the face in tricky places, such as eyelids, were excruciatingly difficult to remove surgically and often left both physical and emotional scars. Liu says itraconazole works in more than half of basal cell skin cancers and allows patients to avoid surgery.

"These results show that we can quickly move our discoveries from bench to bedside," says Liu.

Laboratory scientist **Gregg Semenza** also found success using drug libraries. Nearly 20 years ago, he discovered a cancer target called HIF-1-alpha. It helps cancer cells acquire the oxygen and nutrients they need to survive and grow by stimulating blood vessel growth. But HIF-1 also has a cancer-preventive property. It can block cell division by preventing cells from copying their DNA.

"Cancer cells want HIF-1 around to stimulate blood vessel growth, except when they want to divide," says Semenza. True to form, cancer cells have developed a system for accomplishing these seemingly incompatible tasks. They use two related proteins long known to be involved in cell growth. One protein enters the picture just before cells begin to copy their DNA, attaches to HIF-1 and causes it to be destroyed, removing it as an obstruction to the copying process. After cells finish copying their DNA, the second protein enters and has the opposite effect. It restores HIF-1,

[Discovery]

Gary Schauder, who faced bullets and Agent Orange while serving his country in Vietnam, was not about to let prostate cancer scare him. When Schauder's prostate cancer returned a few years after surgery and continued to grow on treatments aimed at slowing its progress, his wife encouraged him to make an appointment at the Johns Hopkins Kimmel Cancer Center. Under the care of prostate cancer expert **Mario Eisenberger** and nurse **Vicki Sinibaldi** (pictured at left), he began treatment with pharmacological testosterone—an experimental approach developed by prostate cancer researcher **Sam Denmeade**. "I received the drug for the first time about two years ago," says Schauder. "My PSA went from 14 to undetectable. It's starting to elevate a little now, but not much. It's not even up to one." The 72-year-old says he feels energetic and lifts weights for over an hour every day. "It's nice to know I'm coming to a place where I feel like they're helping me and using what they learn from me to help others," says Schauder. "One day, the research they're doing here is going to wipe out this disease." •

PROSTATE CANCER RESEARCHERS **VASAN YEGNASUBRAMANIAN** AND **ELIZABETH PLATZ** FOUND THAT DIGOXIN, A DRUG USED TO TREAT HEART FAILURE, APPEARED TO STOP THE GROWTH OF PROSTATE CANCER CELLS.

LABORATORY SCIENTIST **GREGG SEMENZA** FOUND SUCCESS USING DRUG LIBRARIES. NEARLY 20 YEARS AGO, HE DISCOVERED A CANCER TARGET CALLED HIF-1-ALPHA. IT HELPS CANCER CELLS ACQUIRE THE OXYGEN AND NUTRIENTS THEY NEED TO SURVIVE AND GROW BY STIMULATING BLOOD VESSEL GROWTH.

protects it from destruction and stimulates blood vessel growth.

Semenza found several drugs in libraries that inactivate the HIF-1-alpha-protecting protein that are currently being tested in cancer clinical trials. This research earned him a prestigious Lasker Award in 2016.

Semenza's work intersects with another application of an FDA-approved drug for cancer. In 2010, Nelson and prostate cancer researchers **Vasan Yegnasubramanian** and **Elizabeth Platz** found that digoxin, a drug used to treat heart failure, appeared to stop the growth of prostate cancer cells. Research by Liu and Semenza showed that one of the ways digoxin works against prostate cancer is by targeting and blocking HIF-1. Although early trials with digoxin in prostate cancer did not work against prostate cancer as hoped, the researchers believe the target is a good one and are now studying other drugs that inhibit HIF-1.

Liu and Berger believe there are many other existing drugs that have yet-to-be-realized anticancer properties. "There is no such thing as a perfectly specific drug," says Berger. "There is always some degree of cross-talk."

Liu and Berger attribute some of this early success in finding drugs that may have anticancer properties and moving them to the clinic to the infrastructure that was put in place by **Michael Carducci** and **Philip Cole**, who like **Albert Owens**, **Michael Colvin** and Donehower, helped grow the Kimmel Cancer Center's drug discovery efforts.

Carducci and his prostate cancer colleague **Emmanuel Antonarakis** took itraconazole to their patients, and Carducci, who directs and coordinates clinical research among all Kimmel Cancer Center locations, and a cancer drug discovery expert in his own right, is connecting Liu and Berger to other clinical cancer experts and researchers across all cancer programs and cancer types.

Berger and Liu understand the small bumps along the drug discovery route that can derail a project. There is an art to figuring out how to move a target along and deciphering when a problem is fixable or when it means it's time to abandon a project. Drug discovery is not a linear process.

"If a researcher doesn't get a hit from a drug library, it doesn't always mean the idea is bad," says Berger. "It could be related to the testing assay. A good assay should provide a handful of compounds that may work against the cancer target. If you don't start with a good assay, it could produce 100 hits, the majority of which are false positives, and then you don't know where to start." He and Liu can work with researchers in this case to advise them on the design of a better assay to measure the function, presence and activity of the cancer target.

Liu and Berger have set up a web-based portal that helps cancer researchers walk through questions that help them determine if they have a good target, if there is already a compound that hits the target and whether or not their target is patented by another researcher.

"We want to cast a wide net and allow our scientists to take some chances to see if ideas pan out," says Berger. "At the same time, we built in checkpoints to shift approaches if things aren't working."

His mantra is one borrowed from successful but risky industries: "Fail often, but fail early." His and Liu's goal is to foster a mindset and environment

Trailblazers in Drug Discovery

MICHAEL COLVIN (LEFT) WITH **ALBERT OWENS**

The Kimmel Cancer Center has a long history of moving cancer medicines forward. Whether it was the Cancer Center's first director, **Albert Owens**, and his recruit **George Santos** developing a preparative drug regimen for bone marrow transplant; **Michael Colvin** deciphering how cyclophosphamide works and becoming one of the first to use it in high doses to treat cancer patients; **Ross Donehower**, creating a pre-medication that reduced what seemed like the insurmountable toxicities of paclitaxel, now a mainstay in cancer therapy; or **David Ettinger** ensuring that studies of promising new cancer drugs were made available to cancer patients throughout the U.S. through outreach to community physicians, our experts were trailblazers in drug discovery and development.

After the National Cancer Act was announced in 1971, Johns Hopkins became the site of one of the first comprehensive cancer centers designated by the National Cancer Institute and one of the first to earn a grant to begin clinical trials of new drugs. Our experts quickly earned recognition as they aggressively tested the limits and power of existing drugs, and invented new agents when what we had failed to get the job done.

In 1973, when our Cancer Center opened its doors for the first time, there was no such thing as combined therapies. There wasn't a single genetic mutation or epigenetic change linked to cancer, and no one understood why the immune system was idle against cancer. Today, our experts have led the science in each of these areas and the translation of the science into new drug therapies that target every kind of cancer driver. They continue to be among the best in the world at discovering cancer-promoting changes that can be targeted with therapy, finding or developing drugs that promise to go after the cancer target, and developing tests known as assays that show whether or not the drug is having the intended effect on the target. •

that provides researchers and clinicians the freedom to explore novel ideas. This is a philosophy that has become the signature characteristic of Kimmel Cancer Center research programs, but it also puts into place a mechanism for failing projects to be redirected or stopped before millions of dollars have been spent.

"Academic research brings a lot of people working in a lot of systems to the drug discovery arena," says Berger. "That gives us the ability to generate many fresh ideas and take a lot of shots on goal. We don't expect all of them to pan out."

Even when a project doesn't work out, Liu says, more often than not, it still informs. "Every step along the way contributes. Someone may discover a small molecule that never becomes a drug, but if the early research is good, it will be the foundation for a pharmaceutical or biotech company to come in with its own expertise," he says. "This is important because even if our experts don't see the project all the way through, we have still contributed to the drug discovery process."

This is certainly the case with recent discoveries coming from the Bloomberg~Kimmel Institute for Cancer Immunotherapy. Researchers identified several proteins that cancer uses to shield itself from the immune system. Drugs that block these proteins allow the immune system to see cancer and attack it. There are several proteins involved in this process, but among the most notable so far are PD-1 and PD-L1. Our Cancer Center experts didn't discover the drugs that block these proteins, but the drugs were built upon the researchers' science, and these Cancer Center experts have collaborated throughout the process. Pharmaceutical companies have now developed more than 20 drugs that are FDA approved or in clinical testing that tear down these shields and make cancer cells vulnerable to immune attack. Bristol-Myers Squibb's Opdivo (nivolumab) and Merck's Keytruda (pembrolizumab) are two examples of new FDA-approved immunotherapies that target PD-1 and PD-L1, and are having quite remarkable responses in patients.

"Nivolumab plus ipilimumab was the first immunotherapy combination FDA-approved for any cancer," says **Suzanne Topalian**, a Bloomberg~Kimmel Institute associate director. "Immunotherapy combinations are an active area of research, with several hundred ongoing trials of various combinations." Ipilimumab blocks another shielding protein called CTLA-4. In clinical trials, Topalian says combining the two immunotherapies had a more powerful immediate affect against melanoma skin cancer than either drug but also had increased toxicity.

Right now, the drugs don't work for everyone, but for a small subset of patients, immunotherapy has literally meant the difference between life and death. Nivolumab is FDA approved for treatment of advanced nonsmall-cell lung cancer patients whose cancers progress on standard therapy, and pembrolizumab became the first immunotherapy to gain FDA approval as the front-line treatment for nonsmall-cell lung cancer patients whose cancer cells have a lot of a PD-L1 protein. Pembrolizumab works so well in this PD-L1 subset of lung cancer patients, extending survival well beyond what chemotherapy was able to do, that these patients can now forgo chemotherapy and start with immunotherapy. Recently, a front-line combination of chemotherapy and pembrolizumab was approved for patients with advanced lung cancer, making this the second FDA-approved immunotherapy combination therapy.

Lung cancer expert **Julie Brahmer** led the clinical trial that produced the data used to earn the FDA approval for nivolumab and prembrolizumab. "These results represent a landmark in the history of immunotherapy in cancer. Results showed immunotherapy could be used to treat common cancers and brought it out of the realm of specialized treatment into the broader realm of oncology. Nivolumab has produced the longest follow-up to date of an immune checkpoint inhibitor. Five-year overall survival quadrupled in nonsmall-cell lung cancer, compared with what we would expect from chemotherapy," says Brahmer. "We are doing further studies of these survivors to determine why they had such a good outcome. We also want to better understand which patients can stop treatment at two years and which of them need to continue treatment beyond two years." Many patients continue to have an immune response after the drug is stopped, but right now experts don't have a way to distinguish those who need more therapy from those who can stop treatment.

"Based on these data, I think we can shorten the amount of time patients are treated. But we need to identify those patients who develop immune memory," says Brahmer. "I think we can safely say not all patients need indefinite treatment. We want to personalize therapy. We are continuing to look for biomarkers for response and long-term control."

Helping with the biomarker discovery is Topalian, Bloomberg~Kimmel Institute Director **Drew Pardoll**, and pathologists **Janis Taube** and **Bob Anders**, who developed the test that detects and measures levels of PD-L1 in lung cancer patients. It cemented the FDA approval because it allows doctors to identify patients who are likely to benefit.

Biomarker discovery is pivotal to Nelson's drug discovery and development plans. "The key reason drug research is so costly and frequently fails," he says, "is that often in trials, drugs do not look good because we test them on everyone instead of testing them on the specific patients we think it will help."

The Kimmel Cancer Center is leading the way in precision medicine approaches that use biomarker tests to guide cancer treatment. Just weeks ago, another FDA approval for prembrolizumab hinged on a biomarker test. This time, the approval came for patients with a spell-checklike failure in their DNA called mismatch repair deficiency. This failure allows DNA errors to go uncorrected, contributing to many different types of cancer, including colon, breast, prostate, bladder, ovarian and pancreas cancers. However, these errors also arouse the immune system. Mismatch repair deficiency in cancer was discovered by cancer genetics experts

BLOOMBERG~KIMMEL INSTITUTE DIRECTOR **DREW PARDOLL** (LEFT) AND JANICE TAUBE (BELOW LEFT) DEVELOPED A TEST THAT DETECTS AND MEASURES LEVELS OF PD-L1 IN LUNG CANCER PATIENTS. AS A RESULT, DOCTORS CAN MORE EASILY IDENTIFY PATIENTS WHO ARE LIKELY TO BENEFIT FROM CERTAIN CANCER DRUGS.

LUNG CANCER EXPERT **JULIE BRAHMER** LED A CLINICAL TRIAL THAT PRODUCED DATA USED TO EARN FDA APPROVAL OF A NEW DRUG FOR LUNG CANCER.

PATHOLOGIST **JANIS TAUBE**

[Discovery]

Donald Kirk received a haploidentical bone marrow transplant for lymphoma in 2014. "I can't say enough about everyone here—the doctors, nurses and all of the staff. They are the best," says Kirk, who has a special connection to the Kimmel Cancer Center. His company, Windsor Electric Co. Inc., is doing the electrical construction for the Cancer Center's new Skip Viragh Outpatient Cancer Building. During his seven-week stay in the hospital, he followed the construction from his room in the Weinberg Building. One day, he looked out his window and saw his workers had hung a large banner that said, "Don, Get Well Soon." •

Bert Vogelstein, **Ken Kinzler** and their **Ludwig Center team** in 1993. It was linked to immunotherapy response in 2013 through a Bloomberg-Kimmel Institute collaboration between cancer genetics and cancer immunology researchers. The discovery set the stage for the first-ever FDA approval of a drug based on cancer genetics, not cancer type.

"It's incredibly exciting that we now can prescribe pembrolizumab for patients with mismatch repair-deficient cancers. This could reach 2 to 3 percent of all advanced solid tumor patients. We now have a reason to test for DNA mismatch repair deficiency in almost any disease given the potential for durable clinical benefit," says **Dung Le**, who ran the groundbreaking clinical trial.

These kind of results support Nelson's belief that creating silos for cancer by site is counterproductive to drug discovery and development in the high-tech era that allows us to see the genetic structure of every cancer. Nelson believes what is inside the DNA of a cancer cell may be much more informative for guiding treatment than the area of the body in which it occurs.

"Typically, it has taken about 15 years and $1 billion to discover and develop a drug. We are making discoveries that promise to reduce that to a couple of years and a few million dollars just by changing the way we select patients for clinical trials," says Nelson. "If we begin studying drugs in the patients they are likely to help, everyone benefits. Patients do better, research progresses more quickly and costs come down."

Liu and Berger believe they can get drugs moving forward with a fraction of what it used to cost. A $20 million investment would provide the resources they need to help Kimmel Cancer Center investigators through the laboratory stages of drug discovery and development to screen targets, develop the assays to measure the amount of drug that gets to the target, complete animal studies, and generally support the science needed to figure out if the drug works and how it works.

15

IT TAKES ABOUT **15 YEARS** TO DISCOVER AND DEVELOP A DRUG. BY CHANGING THE WAY PATIENTS ARE SELECTED FOR CLINICAL TRIALS, DISCOVERIES PROMISE TO REDUCE THAT TO A COUPLE OF YEARS.

"Just because you have something that binds to a protein doesn't mean it's going to cross the cell membrane. And just because something crosses the cell membrane doesn't mean it's going to kill cancer," says Berger.

This kind of work is a bit costly, but it is essential to finding new treatments, and it does not get federal funding. "NIH has a very finite pool of dollars, and everyone has a lot of creative ideas they would like funded," says Berger. "To some extent, drug discovery is a bit of a fishing expedition, and that's why NIH and pharma don't like it. It's hard and it's uncertain, but it's also the only path forward."

If there were a guaranteed drug that was sure to work against cancer at the end of the research, everyone would fund it. But medicine isn't an exact science, and the truth is that many times the early work turns up nothing. Still, Berger echoes Liu when he says even the things that fail inform them about the next steps. "In science, you very rarely get to a point where you say 'That was a dead end' or 'That was a waste of time,'" says Berger. "Instead, it's usually, 'Gee, now we know this, and now we should go in different direction and try this.'"

Berger says any first-of-its-kind drug—a potential game-changer—requires the opportunity to follow leads and a willingness to take risks.

CLINICIAN-SCIENTIST DUNG LE HELPS BRING NEW CANCER DRUGS TO PATIENTS THROUGH CLINICAL TRIALS.

However, when it comes to limiting risk, the Kimmel Cancer Center's track record in drug discovery and development makes it a good bet. This success is attributable to its people, says Berger. "We have arguably the most knowledgeable researchers in the fields of cancer genetics, epigenetics and immunology," he says. "Everything we enjoy today comes from basic science conducted 10, 20, 30, 40 or more years ago. Scientific discovery is not linear. The path forward is not always clear, but every finding adds to our knowledge and builds upon the foundation, and we have the experts and the willingness to collaborate that make it possible to put all of the pieces together."

It is this depth of expertise in all of the critical areas of cancer research and a culture that supports sharing information and working together that make it an incubator for new cancer drugs. The Kimmel Cancer Center is also a center that works lean and mean. "It is not the biggest cancer center, but it is, by any form of measurement, one of the most accomplished," says Berger.

The missing ingredient in what would otherwise be a nearly perfect recipe for drug discovery and development is sustained funding. Discovery is slowed because researchers get so far, but they have to stop and apply for more funding before they can move forward. Precious years are lost to the search for funding. "If we want to work quickly with focus, it takes funds that currently don't exist," says Liu. "If we had both, we could do more great things."

Berger and Liu want the Chemical and Structural Biology Program to be that resource for cancer researchers. "We have to make drugs that attack one part of us without attacking another part," says Berger. "Investigators get stuck, and they don't know who to turn to."

The Pipeline

Immunotherapy discoveries are just part of the drug arsenal Kimmel Cancer Center scientists are helping to assemble. Nelson's approach is to go after every vulnerability of the cancer cell. He has been in the business long enough to know that the cancer cell is as complex and crafty as they come. With all of the natural processes of cell division and growth at its disposal, the cancer cell is a master at exploiting these processes to find new ways to cheat death. His vision is to use new technologies and reveal the genetic miscues that drive each person's cancer, and help find or develop drugs that either correct the miscues or shut them down.

There are always going to be a small number of cancers so dependent on a particular genetic miscue that they may only need one approach. This is exciting when it happens, but it doesn't apply to the majority of cancer patients. Most experts agree that cancers, particularly those diagnosed at an advanced stage that have had decades to corrupt many cell processes to their benefit, will likely require combined therapies, including surgery, targeted therapies, immunotherapies and radiation therapies.

"Gene mutations are like fingertips. You cut one off, and the cancer cells just work around it," says **Venu Raman**, who is working on a drug that attacks cancer cells directly and also sensitizes them to radiation.

Nelson believes a combined assault has the potential to disconnect cancer cells from their survival tools and finally overpower them.

RK-33

Raman's drug discovery began with research to understand the effect of secondhand smoke on breast cancer. It led him and his team to develop a first-in-class drug called RK-33. Countless hours in the lab and hundreds of experiments and assays later, Raman and his team have developed and patented a small molecule inhibitor of the DDX3 gene, an exciting first-in-class pharmaceutical.

Research that began in 2005 with funding from the Flight Attendant Medical Research Institute found that a gene called DDX3 was abundantly expressed in cells exposed to cigarette smoke. Raman's lab took a closer look at the gene, and when they blocked its function in animal models, tumors shrank, and the cancer didn't spread.

Tumors that spread from their original site, called metastatic, had the greatest expression of DDX3. "This finding fascinated me because metastatic cancers are the most difficult to treat," says Raman.

The DDX3 gene was already known to be instrumental in the replication of viruses, but no one had developed a way to block it. Working with a medicinal chemist, Raman came up with a series of potential drug compounds designed to inhibit DDX3 activity. After testing different combinations, the 33rd compound hit the target, and RK-33 was born.

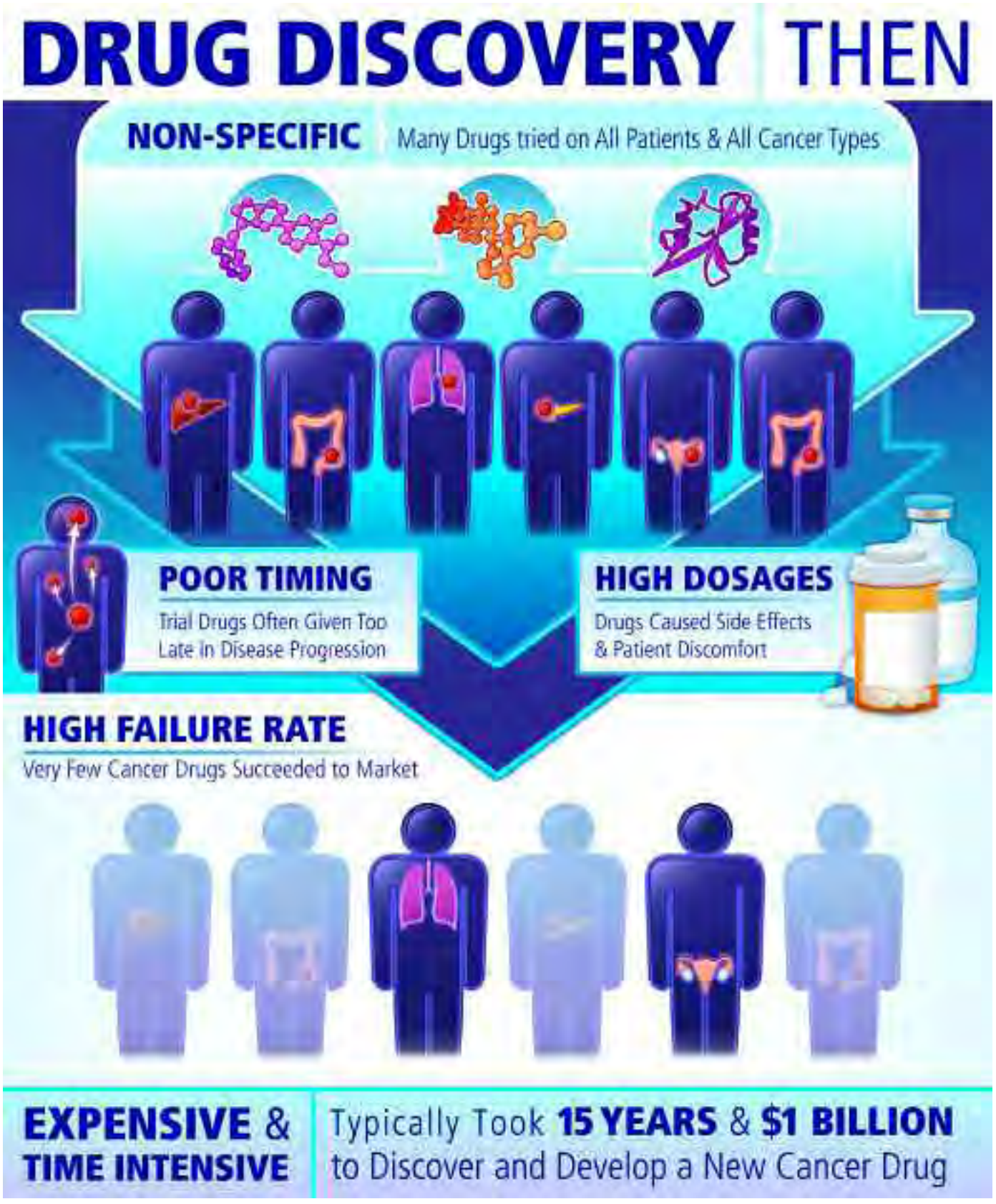
"That was a big day," Raman says. "It's when everything went from theory to reality. We had discovered a new way to attack one of the key enablers of cancerous activity."

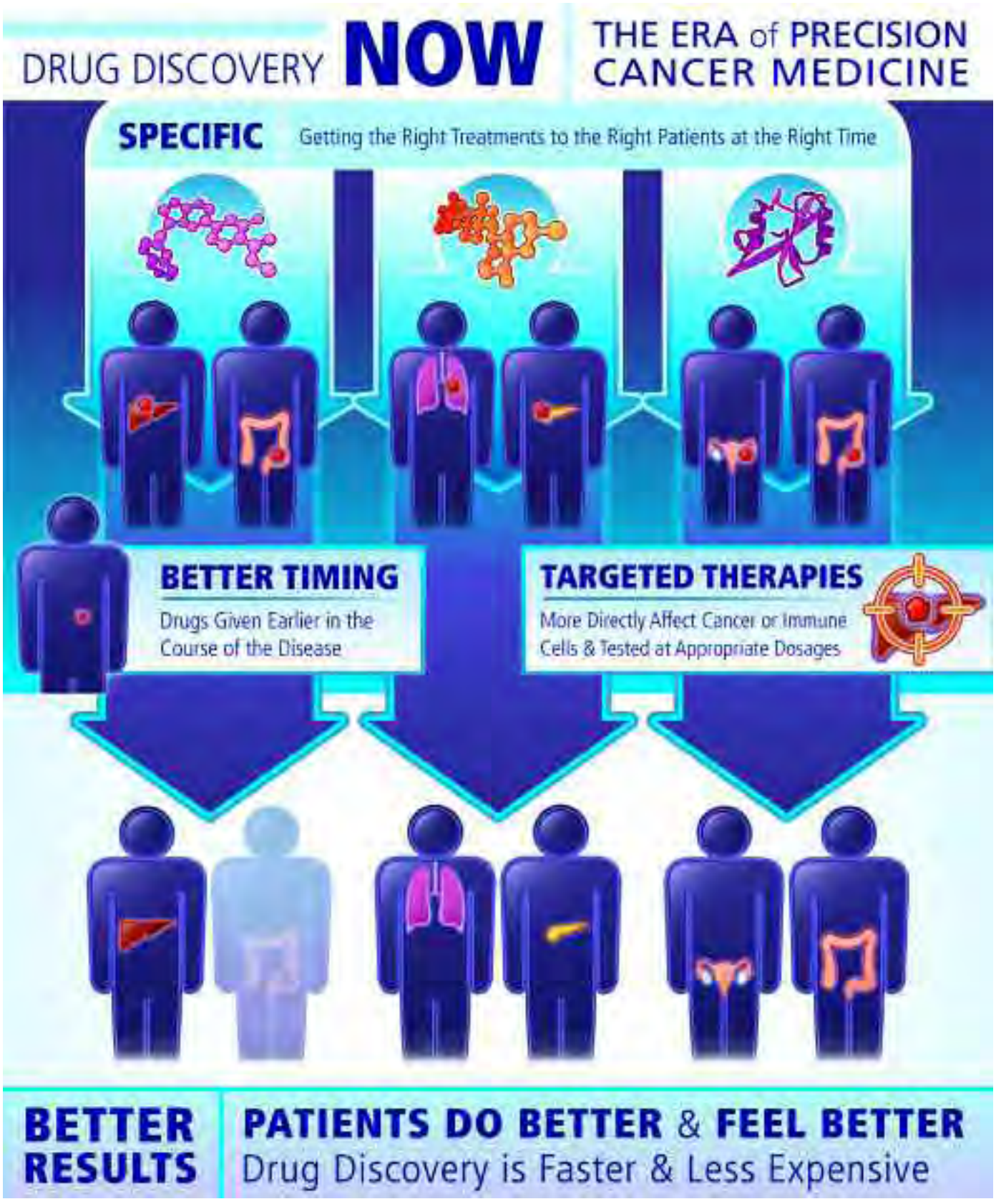
When Raman and his team first tested RK-33 in breast cancer cell lines, it had little effect on normal breast cells with low DDX3 expression. When they tested it in triple-negative breast cancer cells with high DDX3 expression, however, RK-33 easily killed the cancer cells.

"If you imagine your hand as a cancerous tumor," he says, referring to his mutation/fingertip analogy, "many of the drugs that we use to attack cancer act by cutting off a finger. There are still multiple other fingers left, and the rest of the hand can still function and evolve, leading to further spread and even adaptation of cancerous cells. RK-33 acts more like it is cutting off the wrist. When targeted successfully, it prevents a tumor's access to other survival options. Any tumor-sustaining mutations are rendered useless to the cancer cell because it cannot replicate itself."

Since RK-33 attacks overexpressed concentrations of DDX3 with greater intensity and efficacy, it should be toxic to tumors but not to the rest of the body.

VENU RAMAN IS WORKING ON A DRUG CALLED **RK-33** THAT ATTACKS CANCER CELLS DIRECTLY AND ALSO SENSITIZES THEM TO RADIATION. RAMAN'S DRUG DISCOVERY BEGAN WITH RESEARCH TO UNDERSTAND THE EFFECT OF SECONDHAND SMOKE ON BREAST CANCER. IT ALSO APPEARS TO BE ONE OF THE FEW DRUGS THAT WORK AGAINST METASTATIC CANCER CELLS.


DRUG DISCOVERY THEN
NON-SPECIFIC
Many Drugs tried on All Patients & All Cancer Types
POOR TIMING
Trial Drugs Often Given Too Late in Disease Progression
HIGH DOSAGES
Drugs Caused Side Effects & Patient Discomfort
HIGH FAILURE RATE
Very Few Cancer Drugs Succeeded to Market
EXPENSIVE & TIME INTENSIVE
Typically Took 15 YEARS & $1 BILLION to Discover and Develop a New Cancer Drug


DRUG DISCOVERY NOW
THE ERA of PRECISION CANCER MEDICINE
SPECIFIC
Getting the Right Treatments to the Right Patients at the Right Time
BETTER TIMING
Drugs Given Earlier in the Course of the Disease
TARGETED THERAPIES
More Directly Affect Cancer or Immune Cells & Tested at Appropriate Dosages
BETTER RESULTS
PATIENTS DO BETTER & FEEL BETTER
Drug Discovery is Faster & Less Expensive

Studies of the drug's toxic effects on normal cells followed, and as Raman increased the dose of RK-33, it began to work against cancer cells with different levels of DDX3 expression but did not harm normal cells. "We did extensive toxicology experiments," says Raman. "Even at four times the therapeutic dose, it was not toxic in animal models."

Since the project that originally led him to RK-33 involved smoking-associated cancer, Raman decided to also look at lung cancer, and he found it also had significant overexpression of DDX3.

"I thought it was too good to be true," says Raman. "We repeated and repeated the lung cancer studies, and we found out that in sample after sample, this gene was overexpressed. It couldn't be a coincidence."

Further studies showed the gene was overexpressed in many cancer types, including triple-negative breast cancer, one of the most treatment-resistant forms of breast cancer; lung cancer; prostate cancer; sarcoma; and colorectal cancer. With his DDX3 gene target appearing to play a role across cancer types and his DDX3-blocking drug RK-33 patented and in development, Raman went back to the laboratory to decipher exactly how his drug worked at the cellular level.

"The gene is a critical part of the body's DNA repair mechanism," says Raman. "Cancer cells use it to reproduce and maintain the genetic stability essential to their survival." Raman found that blocking the gene with RK-33 not only killed cancer cells directly but also sensitized them to treatment with radiation therapy.

Radiation therapy kills cancer cells by damaging cell DNA beyond its ability to make repairs. Cancer cells that survive treatment do so because they are able to repair their DNA. Raman says RK-33 helps disable this repair mechanism. "If you irradiate cells, their DNA strands break, but over a short period of time, they get repaired. When you add RK-33, the strands remain broken. The cells cannot make repairs."

This finding led Raman to patent his drug as a radiation therapy sensitizer, but the evidence from his research shows it does more. One of the most exciting characteristics of RK-33 is its ability to destroy metastatic cancers—the often-lethal cancers that spread from the original site of a tumor and seed new, treatment-resistant tumors in different parts of the body. Metastatic breast cancers have very high levels of DDX3.

[Discovery]

Tara was diagnosed with advanced sarcoma two weeks before her 4th birthday. **Venu Raman** is working to get his experimental drug, RK-33, into clinical trials. In laboratory studies, the drug works well against metastatic cancer cells, and he is hopeful it will provide new options to patients with advanced cancers, like Tara. •

"Metastasis to the bone, brain and lung is common in cancer, but there are few drugs that have any long-lasting impact against metastatic cancers," says Raman. RK-33 could be the critical difference-maker in the fight against these entrenched, often terminal, cancers.

"Currently, there is no curative treatment for brain cancer metastasis," he says. "It's hard to find a silver bullet for cancer, but because RK-33 is nontoxic and a phenomenal radiosensitizer, there are so many opportunities, including metastatic cancers."

The potential to offer better outcomes to patients with the most difficult diagnoses is what Raman is most excited about. He offers a list of possibilities. "Advanced prostate and colon cancer, sarcoma (bone cancer), brain tumors, inflammatory breast cancer—all these indications are looking promising in multiple cancer models," he says. "We think RK-33 will work in any cancer that requires DDX3. And so far, all these difficult cancers require DDX3.

"My father is a colon cancer survivor," says Raman, "but unfortunately, not every patient responds to our current treatments. This compound represents a chance to change outcomes and save lives, and that's the best of what advanced biological research is about."

Raman is now in the last stages of refining RK-33. Because of its broad application, low toxicity and ability to sensitize cancer cells to radiation therapy, Raman wants a formulation that can be used in both adult and pediatric patients. His goal is to have a drug ready to go to patients in clinical trial within the year.

"We have a lot of pediatric cancer patients at Hopkins, and we are constantly looking to develop solutions that improve their outcomes," says Raman.

Raman draws inspiration from a particular patient. "Tara is a young girl who was diagnosed with a metastatic bone cancer called sarcoma two weeks before her 4th birthday," says Raman. "Currently, there is no standard of care for her disease because all treatments have worked so poorly. Nearly 80 percent of metastatic sarcoma patients relapse within two years of being diagnosed, and five-year survival is less than 20 percent.

"Hopefully this drug will offer new hope and better outcomes for patients like Tara and their families," Raman says. "That's why we're pushing to get RK-33 into human trials as fast as we can."

Despite these promising discoveries, Raman is now facing what is known as the "valley of death." Funding needs escalate rapidly as the drug is tested in humans and then across larger populations, and progress on the new drug will likely slow, or even stop, as he applies for more grants and appeals to more donors. His immediate goal is to obtain enough funding to complete the costly experiments required to file an Investigational New Drug application with the FDA.

[Discovery]

Trina Isaac has advanced colon cancer and is among the many cancer patients who look to clinical trials of promising new drugs to gain an edge against aggressive cancers. “This journey isn’t easy,” says Isaac, who has a young son. “I worry about not being there for him. I’ve prayed, and I’ve cried, but I refuse to let it control me,” says Isaac, whose motto is MMOP —make memories on purpose. “I have cancer, but cancer doesn’t have me.” •

The Flight Attendant Medical Research Institute, Safeway, the Dutch Cancer Foundation, Alex's Lemonade Stand Foundation, TEDCO and other funding partners have brought RK-33 this far, but Raman says that he needs about $3 million to $4 million more.

"Like it or not," Raman says, "the reality of the life sciences industry today is that the pace of getting new drugs to patients is controlled by investigators' ability to find financial partners."

Standing by anxiously are his Kimmel Cancer Center clinical collaborators: radiation oncologist **Phuoc Tran**, pediatric sarcoma expert **David Loeb** and breast cancer expert **Vered Stearns**, who will lead the clinical studies in patients.

"I am so lucky to work in a place like Hopkins. I have a great team working with me. From day one, all of them wanted to help—with no conditions. They are in it for the patients," says Raman. "That's essential because if you are trying to make advances against cancer, you need scientists and clinicians working together. I can't think of an institution that does it better than the Kimmel Cancer Center."

FLT3 Inhibitors

Pediatric Oncology Director and leukemia expert **Donald Small** understands the importance of bridging the laboratory and clinic to bring new drugs to patients. Working with **Mark Levis** in the laboratory and **Doug Smith** and **Patrick Brown** in the clinic, his FLT3 (pronounced flit three) discovery brought a new leukemia drug to adult and pediatric patients.

Small's research of hematopoiesis—how blood cells grow and expand—led him to clone the first human FLT3 gene. Next, he proved that it was very active in acute myeloid leukemia and some cases of acute lymphoid leukemia.

In fact, FLT3 turned out to be the most frequently mutated gene in acute myeloid leukemia. About one-third of patients diagnosed had the mutation—an alteration that made it almost impossible to cure them. "Having a FLT3 mutation reduces the chances of curing an AML patient from about 50 percent to less than 20 percent," says Small.

He had a target in FLT3, and if he could find a drug to neutralize it, Small believed combining such a drug with chemotherapy would improve cure rates for these patients, at least to rates of non-FLT3 AML and potentially even better.

Searching for such a drug proved to be a laborious, time-consuming process. He began by screening a library of more than 4,000 drugs known to target the family of proteins to which FLT3 belonged. He set up 96 wells, filled each one with FLT3-positive leukemia cells and tested each one of the 4,000 drugs to see if any of them killed the cancer cells. One by one, a specific amount of each drug was placed in the wells. "If the color changed, it meant the drug didn't work. If there was no color change, we knew we had an active drug," says Small. When he found a drug that worked, he systematically decreased the amount put in the wells to see how low he could take the drug and still get an anticancer response.

It wasn't high-tech, but at the time, it was the only way to get the job done, Small says. Now, there is an automated drug discovery tool called high-throughput screening that allows researchers to quickly perform millions of chemical, genetic or pharmacological tests, but in the late 1990s when Small began his research, low-tech was the only option for most university-based researchers.

When all of his tests were completed, CEP-701 stood out as the best drug. With a FLT3 inhibitor identified, Levis joined Small and began testing the drug in his laboratory and animal models to help figure out how to best use the drug in patients.

Since the drug had already been tested in clinical trials, this eliminated many of the FDA hurdles needed to move a drug into clinical trials, and Small and Levis partnered with Smith to take it to patients.

As Berger points out, drug discovery is not a single path. There is much back and forth between the laboratory and the clinic, following the science and the clinical data rather than a predetermined and straightforward path to get to the right drug. The essential ingredient of scientist/clinician collaboration is the reason the Kimmel Cancer Center is the perfect environment for drug discovery.

"We're not as big as other places, but we're really, *really* good at working together," says Smith. "We're also outstanding at basic science, clinical research and clinical practice, and that's the translational machinery that makes drug discovery and development possible."

When Smith took CEP-701 to patients, it was a mixed bag of results. The drug cleared leukemia cells out of the bloodstream and, in some patients, out of the bone marrow where new blood cells are made and leukemia originates. But, the responses were temporary, a result not completely unexpected in phase I trials where the sickest of the sick are typically treated.

Levis developed an assay for FLT3, a test that tells if the drug is actually hitting its intended target. "We were excited to see it was killing leukemia cells, and we had an assay to measure it, but we still needed to dig deeper," says Levis.

The group's goal was to get patients into remission using a combination of a FLT3 inhibitor and chemotherapy so they could receive a bone marrow transplant, a potentially curative therapy that replaces the patient's diseased bone marrow with healthy marrow from a donor. Levis' assay proved the drug was hitting its target, but in larger studies, it also showed it had a serious flaw.

The target was a good one, but in many patients, the drug's chemistry allowed the proteins in their bodies to suck up too much of the drug before it hit its target.

Levis went to the inpatient unit, watched patients take CEP-701, got blood samples from patients, carried the blood back to his laboratory himself and then used his assay to test the samples to see if the drug was hitting the FLT3

MARK LEVIS DEVELOPED AN ASSAY FOR FLT3, A TEST THAT TELLS IF THE DRUG IS ACTUALLY HITTING ITS INTENDED TARGET.LEVIS IS CONSIDERED THE WORLDWIDE EXPERT ON FLT3 ACTIVITY. HE, AND OTHERS AROUND THE WORLD, CONTINUE TO WORK ON NEW VERSIONS OF FLT3 INHIBITORS.

PEDIATRIC ONCOLOGY DIRECTOR AND LEUKEMIA EXPERT **DONALD SMALL** UNDERSTANDS THE IMPORTANCE OF BRIDGING THE LABORATORY AND CLINIC TO BRING NEW DRUGS TO PATIENTS. HIS DISCOVERY BROUGHT A NEW LEUKEMIA DRUG TO ADULT AND PEDIATRIC PATIENTS.

CANCER CLINICIAN **DOUG SMITH** CONNECTS DRUG DISCOVERY TO THE CLINIC.

target. If his assay showed the drug was hitting FLT3, Levis knew that patient would respond to treatment.

"The correlation between the drug hitting the target and clinical response was key," says Smith. "You can't get anymore bench to bedside than that."

In that not-so-straight path to a drug, it often takes many chemical modifications to get it right.

Newer formulations of FLT3 inhibitors, built upon Small and Levis' science and other clinical studies, have overcome the limitations of the original drug. Levis is considered the worldwide expert on FLT3 activity. He, and others around the world, continue to work on these better versions of FLT3 inhibitors, and there are several better drugs now being studied in patients. Brown would like to study the newer, more potent versions of FLT3 inhibitors in pediatric leukemia patients, particularly in a subset of leukemia patients he believes would respond well, but currently, studies are limited mostly to adults.

Levis' assay is considered the gold standard, and every major FLT3 drug is sent to him to see if it works.

"We've now demonstrated in patients, through studies here and at other centers, that people who got FLT3 inhibitors—with or without bone marrow transplant—did better," says Smith. "Now we have to continue our clinical trials with the newer versions of the drugs."

Smith says FLT3 inhibitors are being studied in combination with other targeted therapies to see if they have broader uses. "Ultimately, a good FLT3 inhibitor in the right combination therapy could replace bone marrow transplant in certain patients," says Smith. "We would love to give patients a cocktail of a few targeted therapies and no toxic chemotherapy, and eliminate the need for other treatments. That's the goal, but we're not quite there yet."

As a cancer clinician who connects the laboratory to the clinic, Smith finds the drug discovery process one of the most rewarding. "I love having something new to offer my patients," he says. "It's exciting to see a discovery in the laboratory move ahead and become a new drug I can offer to patients."

DON

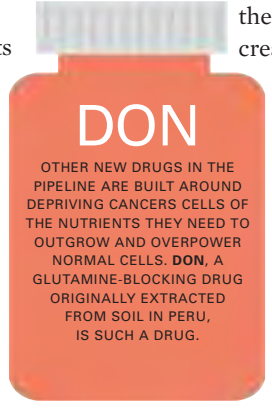
One of the other new drugs in the pipeline is built around depriving cancers cells of the nutrients they need to outgrow and overpower normal cells.

Cancer cells are really just normal cells in hyperdrive. "To grow, cancer cells need fuel—lots of fuel—so they suck up all available nutrients," says **Jonathan Powell**, an associate director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy. The process is called tumor metabolism, and it has become a promising new cancer target.

In essence, cancer cells devour all of the nutrients in their vicinity. They steal glucose and another nutrient called glutamine away from other cells to sustain their growth, creating a position of power for the cancer and, at the same time, weakening normal, healthy cells, including immune cells. While cancer cells are feasting, immune cells are starving and unable to fight the cancer.

"An immunotherapy like anti-PD-1 might do a great job in activating T cells, but when they show up to an environment like this, they can't do their job. They need the nutrients that the cancer is taking," says Powell.

Powell's idea was to create a drug that cuts cancer cells off from the nutrients that feed them so that when immunotherapy is given, T cells show up to a different environment, one that has nutrients available to them so they can energize and go to work against the cancer. "We're not actually targeting the immune system, but rather creating a friendlier environment for the immune system," says Powell.



Coincidentally, Powell and drug development expert **Barbara Slusher** were working together on a student thesis committee. It turned out that the Slusher lab had already been designing drugs for the same target. He shared his idea, and she offered up some compounds for the Powell lab to try.

Slusher was Johns Hopkins trained but had been working for a pharmaceu-

DRUG DISCOVERY EXPERT **BARBARA SLUSHER** AND CANCER IMMUNOLOGY EXPERT **JONATHAN POWELL** ARE COLLABORATING ON A NEW DRUG CALLED DON THAT RE-ENERGIZES IMMUNE CELLS TO ATTACK CANCER.

Drug Discovery a Challenge for Pediatric Cancers

Pediatric cancer expert Patrick Brown recognizes the promise of new drug discovery and development in making progress against cancer, and it's at the heart of his frustration. Brown, who has taken FLT3 inhibitors and other investigational drugs to pediatric leukemia patients, says children are often the last to benefit from new drugs for many reasons.

"Access to drugs and the ability to explore them are the biggest barriers to changing standard of care for pediatric patients," says Brown.

Even when Kimmel Cancer Center researchers make a drug discovery, they typically can only take it so far. "We can't mass-produce drugs, so we usually rely on drug companies to provide drugs for clinical trials," says Brown. The much smaller number of patients with pediatric cancers compared to adult cancers and the risk of something going wrong with a drug being tested in children can make pharmaceutical companies reluctant to provide drugs. This has hindered access to promising new drugs greatly and slowed progress against pediatric cancers, Brown says.

For new FDA-approved drugs, it is possible to get them for study in pediatric patients by purchasing the commercial drugs outright, but costs can vary from $1 million to many millions, and these costs are not typically covered by federal research grants.

There are a few federal laws meant to encourage drug companies to invest in pediatric clinical trials, but Brown says they are largely not very effective. In pediatric oncology, large, multi-institutional studies are the only way to include enough patients to accurately evaluate a new drug, but drug companies are not often willing to support these studies.

"Getting therapies for individual patients in small studies is fine, but if we can't do a large-enough trial to demonstrate survival benefit over standard of care, we can't change standard of care," says Brown. "We are constantly pitching ideas, and experts agree drugs should be tested in kids, but frequently we can't get the drug for our studies."

> "Access to drugs and the ability to explore them are the biggest barriers to changing standard of care for pediatric patients."
> —Patrick Brown

Most large trials are done collaboratively with pediatric oncologists from the 220 institutions that make up the Children's Oncology Group. The group recently proposed a study to look at an immunotherapy drug as upfront treatment for acute lymphocytic leukemia (ALL). "We are completely at the mercy of the drug company as to whether or not it will provide the drug for this study," says Brown."If it says no, which is the most likely answer, the study doesn't happen. Immunotherapy could be a game-changer for kids with ALL, and we're struggling to get the drugs in a timely way. That's very frustrating for us."

Brown says these large studies are really the only way they can begin to move pediatric oncology treatment away from the toxic chemotherapies that can have devastating latent effects in children to the new, short- and long-term targeted therapies that are already benefiting adult patients. Brown and his colleagues try to work with drug companies to form clinical research agreements that include providing drugs for pediatric studies. But, Brown says, "There is not much financial upside for companies to give their drugs away for pediatric clinical trials when they could otherwise sell them."

Still, they keep trying, and occasionally they're successful. Amgen is providing a drug and significant funding to support a clinical trial comparing chemotherapy alone to a combination of chemotherapy and immunotherapy for ALL. "If successful, this study will change standard of care for ALL," says Brown. "There might be some financial payoff for them because ALL is the most common pediatric cancer, but mostly this an altruistic venture on their part."

Celgene is another example. The company is providing one of its drugs, azacytidine, for an infant leukemia study. Infant leukemia is an extremely rare but very deadly cancer badly in need of new drugs, but Brown says it's very difficult to get companies to provide drugs for studies.

Brown says one solution would be an independent funding source that could purchase FDA-approved drugs and provide them for pediatric studies. Kimmel Cancer Center Director William Nelson will explore such a mechanism as part of the Kimmel Cancer Center's drug discovery and development program.

"We all have to be invested in doing better for kids," says Brown. "If there is a way to treat patients and get better cure rates with lower toxicities, we should be doing the studies that make these treatments available to pediatric cancer patients." •

PATRICK BROWN

tical company for the last 18 years, where she was senior vice president of research and translational development. When another pharmaceutical company acquired the business in 2009, Slusher returned to Johns Hopkins with a seasoned team of medicinal chemists, assay developers, and pharmacology/toxicology and pharmacokinetics experts.

She is also founder and president of a world consortium of academic drug discovery centers. Started just three years ago, it has already grown to 150 universities and 2,000 members, reflecting the growing role of the academic researcher in drug discovery. As the pharmaceutical industry has largely withdrawn from drug discovery research, the university researcher has tried to pick up the slack.

"Using existing drugs is one way we expedite drug discovery. It doesn't mean we're done. As in this case, we still have to do medicinal chemistry to get it just right, but it is a faster start."
—Barbara Slusher

"There are so many good ideas and therapeutic target discoveries in academia, but the ability to synthesize drugs against the newly identified targets has not typically existed within universities," says Slusher. "We will never be set up to commercialize drugs. That remains pharma's role, but now we are required to move our basic science discoveries farther along the translational path than we did in the past. As a translational leader, Hopkins is set up to do this—we can synthesize new drugs, show their benefit and take them to a point where a pharmaceutical company becomes interested in picking them up for clinical development."

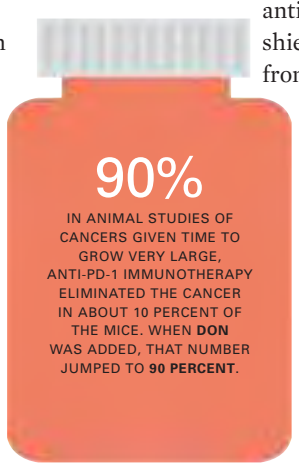
Among the compounds Slusher and Powell began working on was one called DON, a glutamine-blocking drug originally extracted from soil in Peru. In the early assaults against cancer, it was common to use bacteria and other toxins found in soil around the world to make drugs to kill cancer cells. The goal is to give patients the highest dose possible to kill as many cancer cells as possible without harming too many normal cells. It was a delicate balancing act that led to the dose-escalating paradigm that has dominated cancer drug discovery for decades. In the era of precision medicine and targeted therapies, however, that paradigm is slowly but surely shifting.

Earlier versions of glutamine-blocking drugs showed they had cancer-fighting potential but were too toxic to normal cells. Although Powell and Slusher's DON was not new, what Slusher did to make it work was. She changed the drug's chemistry, sticking something to the active drug that makes it inactive as it circulates throughout the body. The drug only becomes active when it gets inside cancer cells. Once in cancer cells, that extra thing she stuck on the drug gets clipped off, and the benevolent passenger traveling through the bloodstream is transformed into a cancer cell killer. The approach is called a prodrug strategy, and the selective activation decreases toxicity to normal cells. Since the active drug is only released in cancer cells, it requires very low doses to work.

"I consider this our real contribution," says Slusher. "We've been able to change the distribution of DON so that they hit more of the target and less normal cells." Slusher plans to use the concept for other drugs. She is already working on a modification to 5-azacytidine, an epigenetic-targeted cancer drug that corrects chemical alterations that support cancer growth.

"Using existing drugs as starting points is one way to expedite drug discovery," says Slusher. "It doesn't mean it's easy. As in this case, we still have to do medicinal chemistry and pharmacokinetics to get it just right, but it is a faster start with higher probability of success."

Powell first envisioned the drug as a way to extend the benefits of immunotherapy to more patients. "I thought it would help in tumors that currently don't respond to immunotherapy," says Powell. It could be given before immunotherapy to create a better environment for T cells to thrive. Targeting tumor metabolism increases the numbers of cancer-fighting T cells, and anti-PD-1 drugs remove a shield cancers use to hide from T cells, creating the perfect one-two punch for an immune assault against cancer.



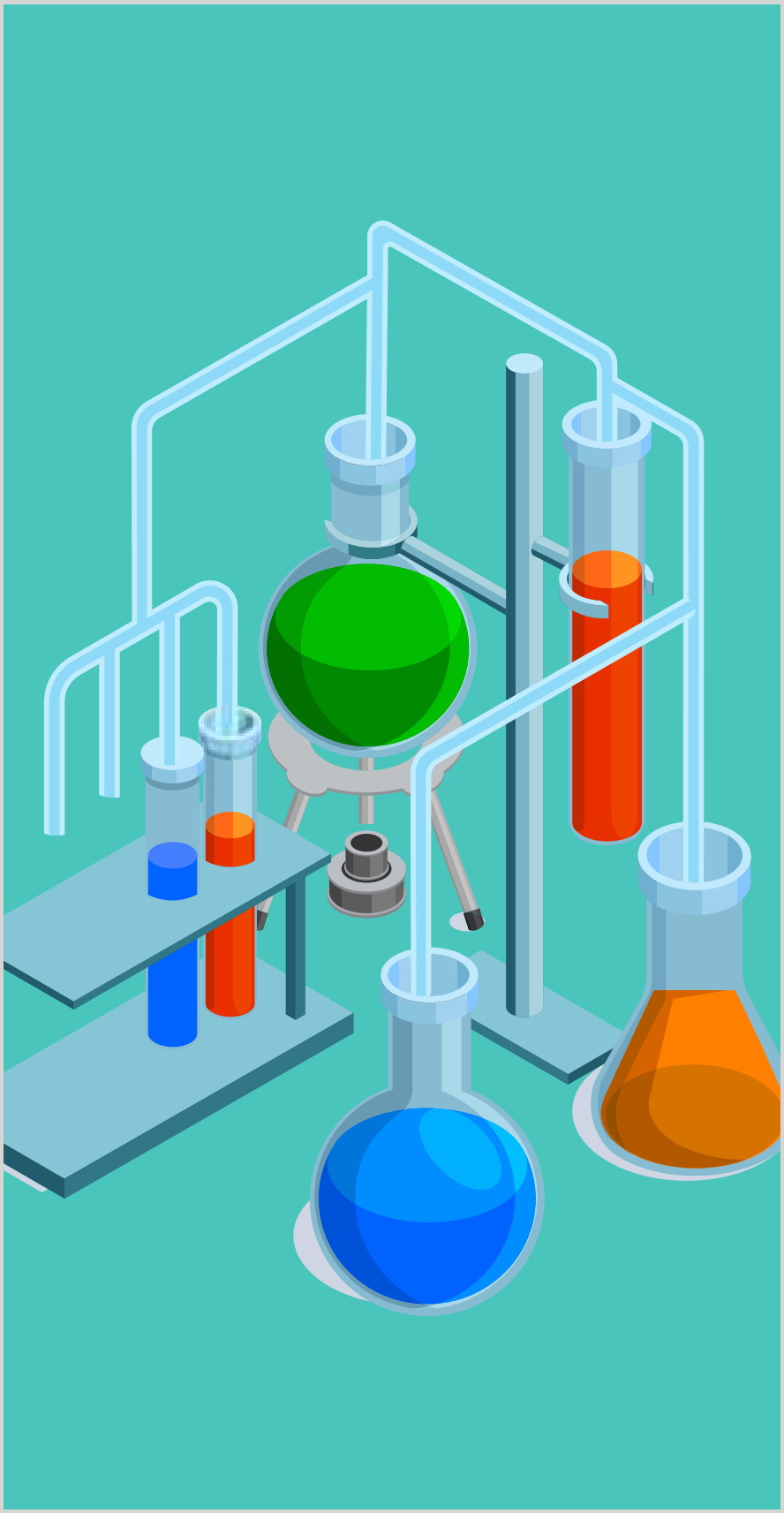
When he studied the drug in animal models, he found it was a potent cancer fighter by itself. "We seemed to unleash the normal immune response just by targeting the nutrients in the microenvironment of the tumor," says Powell. "It makes us think that patients will develop antitumor immune responses when treated with our prodrug alone, but when we add anti-PD-1 to it, we really finish off the job."

Since all cancers are dependent on glucose and glutamine, tumor-targeted DON prodrugs should work across all cancer types. Slusher and Powell were particularly excited to see some of their prodrugs pass the often-impenetrable blood-brain barrier, making it a potential new option for brain cancers, which are among the most treatment-resistant cancers. Powell is optimistic that their new drug will work in many cancers that have been resistant to chemotherapy and immunotherapy. In animal studies of cancers given time to grow very large, anti-PD-1 immunotherapy eliminated the cancer in about 10 percent of the mice. When our DON prodrugs were added, that number jumped to 90 percent.

"We're very excited about taking this drug to patients with cancers that have not responded to other therapies. We think it has the potential to really help them," says Powell. Ongoing studies proved that their modified drug is so

[Discovery]

Allison Uzupus became an oncology nurse two years ago after working as a laboratory researcher for leading pancreatic cancer expert **Elizabeth Jaffee**. "I was really interested in the science, but I knew I wanted a career seeing patients," says Usupuz. "The interaction I have with patients as a clinic nurse is particularly meaningful. It is the realization of everything I did in the lab." Clinic nurses care for patients on many different kinds of drugs and clinical trials, and have the challenging job of staying informed on all of the new drugs and the different reactions that could occur. "There is a lot to look forward to so early in my career," she says. "It's exciting to see these experimental drugs become standard of care and see patients living longer." •



Pharma's New Role

"The world is changing," says **Barbara Slusher**, a drug discovery expert who worked for a pharmaceutical company before coming to Johns Hopkins. "Academic centers are taking on a larger role in drug discovery. We've always been on the front end of discovering targets and on the back end with clinical trials. It's the middle piece of going from a target to a drug that is new for us."

This is another area where the Kimmel Cancer Center is blazing uncharted territory, forming unique collaborations with pharmaceutical partners to fund and advance promising new cancer drugs.

Bristol-Myers Squibb Partnership

A new, five-year collaboration between Bristol-Myers Squibb and the Bloomberg~Kimmel Institute for Cancer Immunotherapy will advance research aimed at uncovering ways that cancer cells hide from the immune system and new immunotherapy-based approaches for killing cancer cells.

"We're at an inflection point of understanding the root causes of response and resistance to immunotherapy, and this collaboration will help propel the research needed to identify ways to expand immunotherapy effectiveness to more patients," says **Drew Pardoll**, Director of the Bloomberg~Kimmel Institute.

It is a natural partnership, as Kimmel Cancer Center experts are on the forefront of immune checkpoint research, uncovering the ways cancer cells hide from the immune system, and Bristol-Myers Squibb has developed several drugs that block these checkpoints and make cancer cells visible to the immune system.

"Our priorities aligned," says Brian Lamon, the global lead for clinical oncology and immuno-oncology in Bristol-Myers Squibb's business development group. "The Kimmel Cancer Center and

Bloomberg~Kimmel Institute are huge intellectual powerhouses. We know they understand what our medicines can do and how they work, but this partnership isn't just about drug development. We are committed to the science. Getting new medicines into patients is the endgame for all of us, but we want to make sure we follow the science. That's where the strength of the Kimmel Cancer Center makes a difference. There is pretty broad expertise to do a lot of different things, and the ability to put it all together. These are complex, dynamic systems, and Hopkins has the expertise to take it on."

The collaboration will include laboratory research and clinical trials to decipher why immunotherapy works in some patients and not others. Combined immunotherapies and their use as first-line treatments are among the approaches being studied.

Celgene Partnership

The Kimmel Cancer Center was one of four National Cancer Institute-designated comprehensive cancer centers selected to participate in a unique cancer consortium aimed at speeding up the process of cancer drug discovery. The collaborative nature of the consortium should expand access to expertise, eliminate duplication of effort and increase the payoff—to the private sector, the cancer centers involved and, most importantly, to patients worldwide. The cancer centers at the University of Pennsylvania, Columbia University Medical Center and the Icahn School of Medicine at Mount Sinai are the other consortium members.

Through team science, the participating institutions will have access to financial resources from Celgene Corporation and will share in revenue generated from discovery. Together, the participating institutions initially received $50 million —$12.5 million to each—but Celgene is making $300 million to $1.5 billion available to the consortium to advance research. All consortium member institutions will share in any revenue generated from discoveries, with the cancer center or centers responsible for discoveries receiving the largest return. The Kimmel Cancer Center was selected for the consortium for its long history and pioneering roles in new drug discovery and clinical research.

"The world is changing. Academic centers are taking on a larger role in drug discovery. We've always been on the front end of discovering targets and on the back end with clinical trials. It's the middle piece of going from a target to a drug that is new for us."
—Barbara Slusher

Kimmel Cancer Center Director **William Nelson** and Cancer Chemical and Structural Biology Program leaders **James Berger** and **Jun Liu** will direct efforts and serve as liaisons to the consortium. Nelson sees opportunities for private philanthropy to further accelerate discoveries made through the consortium.

AbbVie Partnership

Last December, AbbVie, a global biopharmaceutical company, signed a five-year collaboration agreement with Johns Hopkins, with the goal of advancing cancer drug discovery at both organizations. The agreement focuses primarily on lung, colorectal, breast, prostate and hematological cancers.

The partnership is a bit of a reunion, as AbbVie's cancer division is managed by Gary Gordon, a former Johns Hopkins researcher. "As an alumnus and a former faculty member of the Johns Hopkins University School of Medicine, I know from my own experience that we will be able to combine AbbVie's expertise in oncology with some of the most talented academic researchers in the field of medicine today," says Gordon, vice president of oncology clinical development.

The agreement gives Kimmel Cancer Center physicians and scientists access to explore new therapies developed by AbbVie for use in preclinical research funded by the collaboration. In addition, the relationship includes opportunities for research and development teams from both organizations to work closely to promote scientific knowledge exchange. AbbVie also gains an option for an exclusive license to certain Johns Hopkins Medicine discoveries made under the agreement.

"The importance of cancer research is critical to developing new therapies that could have life-changing implications," says Kimmel Cancer Center Director **William Nelson**. "Opportunities to advance science and further research help move us in a direction to yield positive outcomes."

As part of the collaborative agreement, a joint steering committee consisting of representatives from each organization will determine the research projects that the collaboration will undertake. **Michael Carducci, Jonathan Powell** and **Vasan Yegnasubramanian** are representing the Kimmel Cancer Center. Researchers from Johns Hopkins and AbbVie will also participate in an annual symposium to discuss their joint research and evaluate potential new projects. •

cancer specific that it only releases its power in cancer cells, virtually remaining nontoxic in all other cells. Their research also shows signs that the drug may also sensitize cancer cells to radiation therapy.

Slusher and Powell hope to have the drug in clinical trials in two years. To get there, they will need to complete additional studies to get the FDA approval needed to take their investigational new drug to patients. Deerfield Management recently announced plans to invest $40.5 million in Dracen Pharmaceuticals, Inc., a start up company founded by Powell and Slusher to develop DON and other cell metabolism-tartgeting drugs.

Powell echoes Berger's and Liu's emphasis on more resources to help investigators bridge the funding gaps that limit drug discovery. "Until we got dedicated funding from the Bloomberg~Kimmel Institute, we were funding this research with bake sales, cobbling together small amounts from different places to keep it going," says Powell. "If we had a fully supported program for drug discovery, it would make a huge difference in speeding progress."

The collaborative environment at Johns Hopkins makes it a fertile ground for scientific progress. "The value of discovery is underrated. It's messy and risky, but it's essential," says Powell. He points to a time early on in the research when one of the compounds wasn't working at all in the laboratory studies. Powell was disappointed until he received a call from Slusher who, unaware of his laboratory outcomes, advised him not to use the compound. She spotted a problem with her compound's stability and knew it wasn't going to work. "Her team on the drug discovery side and our team on the cancer research laboratory side came to the same conclusion independent of one another and provided extra confirmation for what we were seeing. Her observation of the drug confirmed what I was seeing in the laboratory, and my observation in the laboratory confirmed that she was right about the problem she spotted with the compound," he says.

"That's the beauty of science. You put people together with diverse skills, and they find something unexpected," says Powell. "There is no formula for it. You just put people together and let them work. This kind of collaboration thrives in the Kimmel Cancer Center."

[Discovery] In 1999, when **Janice Paulshock** (second from right) was diagnosed with ovarian cancer, her doctor gave her no hope. She worried that she would never see her 8-year-old daughter and 6-year-old twins grow up. She decided to seek a second opinion at the Johns Hopkins Kimmel Cancer Center. Her doctors assured her there were many treatments they could try, including a promising drug called paclitaxel. Janice received the drug in 1999 and again in 2001 when her cancer came back. She has been cancer-free since 2008. She has seen her children grow up and graduate from high school and college. Last year she celebrated her oldest daughter's wedding, and in 2018, she will become a grandmother.

"Knowing that there are doctors always looking for new and better cancer drugs gives patients like me such hope," says Janice. "They never gave up on me, and I'm alive because of that. It's the greatest gift." •

MARIKKI LAIHO DEVELOPED A DRUG THAT PREVENTS CANCER CELLS FROM ACCESSING A CELLULAR MACHINERY THEY NEED TO SURVIVE.

BMH-21

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

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

The drug goes after a kind of cellular machinery called the RNA polymerase 1, or POL1. The genetic instructions in our DNA are read out by RNA polymerases. Cells have three main ways—POL 1, 2 and 3—to read the instruction manual that is our DNA and help convert those instructions into protein-based actions that are dictated by genes. Errors in the genetic code, known as mutations, alter how proteins are formed and function, and ultimately how cells behave. POL2 is studied most in cancer because it executes the primary program that leads to the defective proteins related to the majority of cancer mutations identified to date. The other two polymerases, however, provide essential molecular tools that help make the actual proteins.

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

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

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

Laiho discovered a drug called BMH-21 from a drug library screen and then worked with her research team to identify the target, POL1. Now Laiho is working with Johns Hopkins medicinal chemist James Barrow to refine it. She

BMH-21, A CANCER DRUG NOW BEING STUDIED IN PROSTATE CANCER AND MELANOMA, APPEARS TO WORK IN MANY OTHER CANCER TYPES.

was surprised by how well the drug worked in preclinical proof-of-principle studies. "Without this transcription machinery, cancer cells couldn't recover," says Laiho. "They cannot function."

BMH-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. "We have been able to confirm that BMH-21 works by binding to DNA and are very near the optimal stage of drug development," says Laiho. "Typically, many revisions to the lead molecule are required before it is ready for clinical studies. We are very excited because that is not the case with our drug, and that means we are closer to the clinic than we could have ever imagined."

With most of the science in place, the research could be translated into a new treatment in a little over a year. Still, Laiho and team face some hurdles. She needs funding and a pharmaceutical partner to make the leap from laboratory to clinic. Bluefield Innovations, a Deerfield Management and Johns Hopkins University collaboration aimed at supporting the commercialization of early stage drug research at Johns Hopkins announced that it will take on Laiho's drug as its first project. A prestigious Harrington Discovery Institute Scholars-Innovator Award, the Patrick C. Walsh Prostate Cancer Research Fund and the Allegheny Health Network have also provided much-needed funding to help move her drug to the clinic.

"It has taken a long time to get here because this was uncharted territory for me," says Laiho. "From the day I had my molecule, I was walking around asking about how to do the molecular modeling, how to make derivatives, and how to do a PK experiment. I had an endless line of questions."

PK, refers to pharmacokinetics. Literally translated, it means movement of drugs—how a drug gets into the bloodstream and then travels to tissues and organs, how the body breaks the drug down, how long it stays in the body and how the body gets rid of it. Experiments directed at understanding how a drug moves through the body and what it does are an essential part of new drug development.

The collaborative nature of the Kimmel Cancer Center certainly worked in Laiho's favor, and she found answers to her PK experiments questions and other questions by making connections with experts, but this took time. She believes Nelson's vision for the drug discovery program in the Kimmel Cancer Center represents a complete package of all the necessary elements that would speed drug discovery and development.

"We need financial support, but we also need knowledge support," says Laiho. "The knowledge already exists here, so we're one step ahead already. We just need to bring all of the elements together."

As Laiho inches closer to moving her drug to patients, one of the things she is most excited about is its application across many cancer types. "Even though we are looking at prostate cancer and melanomas now, BMH-21 appears to work in many solid tumors with high dependency on the POL1 pathway," says Laiho. "The more a tumor depends on this pathway, the better this treatment should work." She hopes to be able to obtain enough support to soon launch clinical trials in prostate cancer patients who have exhausted all other treatment options and to make the necessary modifications to BMH-21 to expand studies to other cancers.

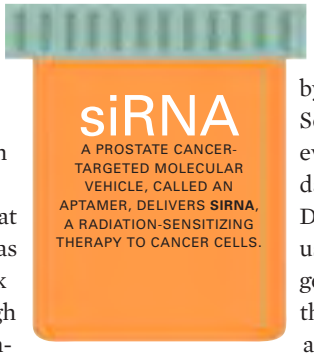
Aptamers and siRNA

The merging of two discoveries may provide a novel way to deliver cell destruction to prostate cancer. At the center of the research are two things familiar only to scientists—aptamers and small interfering RNA (siRNA).

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

Aptamers aren't designed to have a particular shape or binding site for a target protein. Instead, they are selected from a pool of billions of different molecules by a stringent and complex process. When Lupold first took on the project as a graduate student, it took him five years to drill down to just the right chemical formulation. Today, this can be chemically synthesized in just a few days.

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



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

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

Their treatment worked well in animal models, and aptamers are already FDA approved for other medical purposes, so Lupold and DeWeese do not anticipate

PROSTATE CANCER EXPERTS **THEODORE DEWEESE** (LEFT) AND **SHAWN LUPOLD** MERGED THEIR INDIVIDUAL DISCOVERIES TO DELIVER DESTRUCTION TO PROSTATE CANCER CELLS.

"Despite its difficulty, drug discovery thrives in our unique environment of collaboration and unparalleled expertise in virtually every area of bench-to-bedside cancer research. Discoveries in these fields are providing the cancer targets that are driving new drug development and precision medicine."
—William Nelson

PROSTATE CANCER EXPERT SAMUEL DENMEADE USED A PHARMACOLOGIC VERSION OF TESTOSTERONE TO TRICK CANCER CELLS INTO DEATH.

any safety problems. To move the therapy to clinical trials, they will need about $1 million to outsource the production of clinical-grade aptamers and to evaluate them in FDA-relevant preclinical models.

DeWeese says their siRNA aptamers are unique to Johns Hopkins and the first to sensitize cancer cells to radiation. The current version is specifically targeted to prostate cancer, but he says with an adjustment to the chemical GPS, they can be adapted to target essentially any cancer.

Testosterone as a Drug

The male hormone testosterone can feed the growth of prostate cancer, but in an interesting twist, when given in a very specific way, it may also cause its demise.

Drugs that block the action of testosterone are commonly used to treat men with advanced prostate cancer therapy. Cutting off the supply of testosterone to the cancer works for a time, but eventually prostate cancer cells figure out a way around it and begin to grow again. Other drugs work at the molecular level to cut off prostate cancer cells' access to testosterone, but their impact is temporary and comes with unpleasant side effects.

"Men who have long-term hormone ablation have a good response initially, but eventually they become resistant to therapy, and then there aren't many options left for them," says prostate cancer expert **Samuel Denmeade**. These are the men most at risk of dying from prostate cancer.

With testosterone viewed as a fuel for prostate cancer, most researchers are reluctant to explore it as potential therapy. However, what Denmeade and fellow prostate cancer researcher **John Isaacs** envisioned was different, and it all came down to the delivery.

Taking a play right out of cancer's playbook, Denmeade and Isaacs figured out what prostate cancer cells were doing to survive hormonal therapy and then beat them their own game.

After prolonged treatment with testosterone-blocking drugs, prostate cancer cells adapted to living with low levels of the hormone by ramping up the activity and amount of receptors within the cell surface to suck up every bit of testosterone available.

With prostate cancer cells in this state, adapted to an environment with low levels of testosterone, Denmeade wondered what would happen if he flooded the cancer cells with a short burst of high-dose testosterone, using the hormone like a drug.

"If we give testosterone acutely through injection to cause a sharp rise in the hormone, prostate cancer cells won't like that, and some will die," says Denmeade. "Prostate cancer cells might be killed by the hormone shock, and the cells that survived would make fewer receptors, making prostate cancer cells vulnerable once again to hormone-lowering therapies."

2/3

ABOUT **TWO-THIRDS** OF MEN TREATED WITH A MONTHLY INJECTION OF TESTOSTERONE TO HELP BOOST THEIR TESTOSTERONE LEVELS RESPONDED WELL TO THE THERAPY, HELPING KEEP THEIR PROSTATE CANCER STABLE.

At first glance, it seems paradoxical to give testosterone to a prostate cancer patient, but Denmeade and Isaacs say this approach is very different from the chronic, ongoing supply of testosterone that naturally occurs in men or testosterone replacement therapy. "It's pharmacologic testosterone, not physiological testosterone," says Isaacs.

Prostate cancer cells are not expecting an intense dose of testosterone, and they don't know that it's a short burst. Cancer cells that survive will adapt again, this time turning down the activity of those cell surface testosterone receptors. "They will downregulate their receptors at a time when the drug is wearing off, so we will see a period of low testosterone, low receptor, and that's not good for cancer cells," says Denmeade.

As the cells are continually challenged with these short bursts of testosterone, they are constantly adapting levels of cell surface receptors up and down. "We are taking the cancer cells' options out of play by making the testosterone levels rise and fall rapidly," says Denmeade.

Denmeade turned the idea in a clinical trial of testosterone as a prostate cancer drug therapy. Following a pilot study funded by the One-In-Six Fund, the National Institutes of Health, and a $5 million Transformative Grant from the Department of Defense, he began to perform two studies—one at one at the Kimmel Cancer Center, and another at 18 sites across the U.S. Both clinical trials in asymptomatic men with prostate

[Discovery] **Riley**, 11, has a slow-growing and rare benign brain tumor called a pylocytic astrocytoma. She calls her tumor Roger, and says, "I kicked his butt." The tumor, located between her optic nerve and pituitary gland, can't be taken out surgically. It will require lifelong monitoring, and drug therapy and radiation therapy when she is older—to keep it from growing into her optic nerve and affecting her vision. This is the kind of tumor that **Sonia Franco**'s minibrain model could impact, providing new information about how they grow and the therapies that may work best. •

Early Phase Clinical Trails

Michelle Rudek runs the Kimmel Cancer Center's Analytical Pharmacology Core. Like other drug discovery laboratories, Rudek leads a team that conducts tests to see how promising new drugs travel through the body; how they are absorbed, distributed and metabolized; how long they stay in the body; and ultimately what effect they have on cancer cells. However, Rudek's lab is different from others in that it supports cancer drug discovery throughout the Kimmel Cancer Center, Johns Hopkins and beyond, with as many as 90 projects with varying degrees of complexity ongoing at any time. She and Michael Carducci lead the lab's role in testing drugs being used in the National Cancer Institute's (NCI) Experimental Therapeutics Clinical Trials Network, and her lab also supports NCI's Adult Brain Tumor Consortium and AIDS Malignancy Consortium.

Rudek's personal research is focused on helping cancer patients who have other health conditions. She deciphers and manages drug interactions and dosing so that cancer patients taking medications for other health conditions, such as AIDS malignancies, or who have liver or other organ dysfunction can safely receive cancer drugs.

"It's so rewarding," says Rudek, who is one of the few drug experts doing this kind of work. "We're changing the standard of care for these patients and making it possible for more patients to participate in cancer clinical trials."

Rudek was recently honored with the NCI's Michaele Christian Oncology Development Lectureship and Award. The award recognizes her leadership role in translational research and clinical pharmacology in early-phase clinical trials and special populations. She is the first nonphysician recipient.

MICHELLE RUDEK (LEFT) LEADS A DRUG DISCOVERY LABORATORY AND HELPS MAKE IT POSSIBLE FOR PATIENTS WITH UNDERLYING HEALTH CONDITIONS TO PARTICIPATE IN CANCER CLINICAL TRIALS.

[Discovery] **Cindy Lersten** has spent more than a decade of her 50 years battling cancer. Her journey began in 2001, when she was diagnosed with melanoma. The cancer stayed in check for years—until 2012, when it returned and began to spread. "I thought that was it," recalls Lersten, a mother of four. "I thought my life was over." She traveled to another hospital for immunotherapy. The treatments worked for a time, but in 2017, it came back. She then came to the Kimmel Cancer Center for additional treatment. New studies of combined immunotherapies—trials that tested two, and sometimes even three, different drugs had begun. She participated in a clinical trial of one of these immunotherapy combinations and also opted for surgery. Currently, there is no evidence of cancer. "The first treatment bought me time so that when my cancer came back, there were new options for me," says Lersten. The combination of surgery and new drugs are holding her cancer at bay once more. It is working so well for Lersten that she was healthy enough to climb Mt. Fuji with her 15-year-old son. "These drugs gave me renewed hope," she says. •

cancer that has progressed on hormone therapy were designed to see if a monthly injection of testosterone to make the testosterone level rise sharply for about a week would kill cancer cells. Denmeade says about two-thirds of the men treated responded well to the therapy, at least keeping their prostate cancer stable.

But Denmeade noticed that some of the men treated were resensitized to hormone therapy. That observation was the impetus for his Transformer Study, a new clinical trial to see if giving testosterone in sequence with hormone therapy could prevent or reverse hormone treatment resistance.

One patient in the study had his cancer completely disappear for two years. Denmeade is now looking for biomarkers that predict which patients will respond best to the testosterone therapy. Prostate cancer expert **Emmanuel Antonarakis** identified a subset of patients with a variation in their cell surface receptors that predicts a more aggressive and resistant type of prostate cancer. Denmeade's testosterone treatment may convert it to a less aggressive form of cancer.

A new study, called the Batman Study, is funded by the Patrick Walsh Foundation, and is helping Denmeade and colleagues look more deeply into the specific molecular and cellular mechanisms that make this therapy work. With the exception of patients with prostate cancer that has spread to the bone, the short burst of testosterone makes most men feel better. "Men were hugging me because they felt so good. People are clamoring for it," says Denmeade. "We get emails from men all over the country and the world."

Denmeade says they are still learning about the best way to safely give the therapy. "So far, the side effects have been low grade, as long as the treatment is limited to men who are asymptomatic without any pain due to prostate cancer," he says. "In some cases, the testosterone therapy makes men feel increased energy, less fatigue and restored sexual function." To date, 150 men have been treated with varying responses. "We have some patients whose PSA drops after treatment and their scans get better; we have others whose PSA doesn't drop and even have some initial rises. For most patients, their prostate cancer is at least held in check," he says. PSA stands for prostate-specific antigen. Tests that measure rising levels of PSA in the blood are used to screen for prostate cancer.

Denmeade is studying cells from the one complete responder more closely in hopes it may provide critical clues. "If we can understand what happened in this one guy, it would provide a wealth of information," he says. One possibility is that the up and down of the testosterone attracts the attention of the immune system, which is always on patrol for things that look out of the ordinary. Deciphering what underpins these varied responses could reveal biomarkers that will help them decide who are the best candidates for the treatment and how long to give it.

"There has been a groundswell of interest," says Denmeade. "Right now, we have plenty of anecdotes and some evidence of how it works, but we need to do more research and test it in more patients."

The treatment with generic testosterone is a bargain at about $100 a month, but lacking a pharmaceutical partner, Denmeade and Isaacs are struggling to find funding to do additional combination studies. "Since we are using a generic form of testosterone we may have difficulty getting support from pharmaceutical companies," says Isaacs. "So for now, it remains a completely homegrown project."

[Fusions]

Artist **Maria Lanas** accompanied her father-in-law to the Kimmel Cancer Center when he received a new experimental drug for his advanced melanoma cancer. "The infusions took several hours, and as I watched the drops slowly go down the tube into his body, I began to imagine the fight that was taking place in his body as the drug mixed with his blood," says Lanas. She calls the artwork infusions. "It represents the life and hope these new drugs offer to cancer patients, so I used the brightest colors on my paint palette," says Lanas. She gave the paintings as gifts to the doctors and nurses who cared for her father-in-law, and one was auctioned to raise money for cancer research at the Kimmel Cancer Center. •

New Models of Discovery

An important element of drug discovery is the scientific models used to study drugs. Increasingly, the laboratory models scientists use to determine if, how and why a drug works don't work well in cancer. To address that weakness, Kimmel Cancer Center investigators are pushing the boundaries and developing inventive new ways to study drugs.

"Minibrains"

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

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

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

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

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

Unexpected Lead on a New Brain Cancer Drug

After treating mice with the anti-parasitic drug mebendazole for a pinworm outbreak, neurosurgical oncologist **Gregory Riggins** noticed they could no longer grow brain tumors. The observation led Riggins to take a closer look at the drug as a possible new therapy for brain cancer. His research revealed the drug blocked blood vessel growth in tumors, slowing their growth. Riggins and team modified the drug's formulation to make it more effective against cancer and began a clinical trial of the drug in 21 glioblastoma patients. The drug was well-tolerated by patients in the early study, leading to another clinical trial in children.

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

COMPLEX, ORGANIZED SPHERES OF HUMAN NEURAL AND NERVE CELLS ARE DUBBED ORGANOIDS OR MINIBRAINS. THEY CANNOT THINK OR LEARN LIKE A HUMAN BRAIN, BUT THEIR STRUCTURE IS SIMILAR ENOUGH TO THE ANATOMY OF A DEVELOPING BRAIN THAT MOLECULAR RADIATION SCIENTIST SONIA FRANCO BELIEVES THEY CAN BE USED TO REPLICATE HOW PEDIATRIC BRAIN CANCERS NATURALLY GROW AND SPREAD. SHE IS USING THE MINIBRAINS TO STUDY DRUG AND RADIATION TREATMENTS.


JOHNS HOPKINS
Sonia Franco, MD
Radiation Oncol

Drug Discovery Revolutionized Bone Marrow Transplant

John Hilton's and **Michael Colvin's** research more than three decades ago to decipher how the popular anticancer drug cyclophosphamide worked against cancer paved the way for major advances in bone marrow transplantation. The Kimmel Cancer Center's first director, **Albert Owens**, and bone marrow transplant program leader **George Santos** performed research that used the drug at high doses instead of total-body radiation to destroy diseased bone marrow before transplanting patients with healthy donor marrow. The first successful bone marrow transplant followed high-dose cyclophosphamide.

Their early research also hinted at the usefulness of the drug after bone marrow transplant to limit the major complication of the procedure, graft-versus-host disease (GVHD), where the new donor immune system attacks the bone marrow and other normal tissues. These findings were pursued years later by Santos-trained bone marrow transplant expert **Richard Jones** and his colleagues."Post-transplant cyclophosphamide revolutionized the field," says Jones, director of the Cancer Center's Hematologic Malignancies and Bone Marrow Transplant Program. His team continued the early cyclophosphamide research, expanding the drug's ability to limit GVHD without harming the blood stem cells that give rise to new, healthy blood cells. As a result of this work, today it is possible to do transplants in all patients, even those who do not have matching donors. GVHD limited the ability to do mismatched transplants in the past, but now, it is so well-managed—in large part due to cyclophosphamide—that nearly 95 percent of patients survive transplant, and it results in unmatched transplants that are the same as matched transplants.

Today it is possible to do transplants in all patients, even those who do not have matching donors. The immune side effect is so well-managed that more than 95 percent of patients survive.

African-Americans, Hispanics and other minorities, who have historically been excluded from transplants because of the inability to find matching donors, now have the highest accrual to bone marrow transplant clinical trials in the history of the therapy. Jones is excited about new research on the horizon, including combining transplant for solid tumors with anticancer agents to enhance immune reaction against cancers.

A novel twist in prostate cancer research includes using bone marrow donated by daughters of patients. Women do not have prostates, so the immune system of the female donors will never have seen prostate cancer, a disease that only occurs in men, and should immediately recognize the cancer cells as foreign invaders. "All of these advances are possible because of cyclophosphamide," Jones says. •

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

Franco is collaborating with Kimmel Cancer Center at Sibley radiation oncologist and brain tumor expert **Matthew Ladra** to perfect her model. Ladra received funding from Children's National Pediatric Cancer Center to explore the effects of radiation therapy on pediatric tumors and the surrounding normal brain. The joint effort is the result of a unique collaboration between pediatric oncologists and surgeons from Children's National and radiation oncologists at the Kimmel Cancer Center to create the first dedicated pediatric radiation oncology program in the national capital region.

Ladra is sharing tumor samples with Franco she can implant in her minibrains.

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

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

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

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

EMT and Harmine

Cancer cells are crafty—just ask clinician-scientist **Phuoc Tran**, who has identified a new drug and created a new model to study it.

In his current research, he is studying how cancer co-opts an exquisite process

"We need to provide the necessary drug development tools, resources and funding for our scientists and doctors, and more rapid access to new cancer drugs for our patients."
—William Nelson

of human development to undergo its most lethal transformation. A process that normally directs an embryo to grow from a single cell into a fully developed human being may be the same one used by cancer cells to invade other parts of the body.

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

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

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

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

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

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

The Next New Cancer Treatments

Cancer is challenging because it is very different from every other disease. It is part of our own cells. "We have to make drugs that attack one part of us without attacking another part," says Liu. He and Berger look at the ideas and discoveries coming from Kimmel Cancer Center experts, including recent advances in immunotherapy, and they wonder where the next revolutionary cancer treatment will come from.

"There is something waiting there," Berger says. They think of themselves as scouts, surveying the clinics and the laboratories of the Kimmel Cancer Center for promising new therapies they can help researchers push forward. "We are fortunate to work in a place where so many are pursuing interesting science," he says. "We want to capture the power of this science and be a bridge between laboratory discoveries and new therapies.

"We still have cancers that don't have good therapies. We know there are solutions. We just have to find them." •

Drug Discovery

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MAGNET RECOGNIZED

Coming in the next issue:

The Johns Hopkins National Proton Therapy Center at Sibley Memorial Hospital

The Kimmel Cancer Center is becoming one of only 20 proton therapy centers in the nation, providing a form of targeted radiation treatment that zeroes in on tumors while sparing normal cells.