

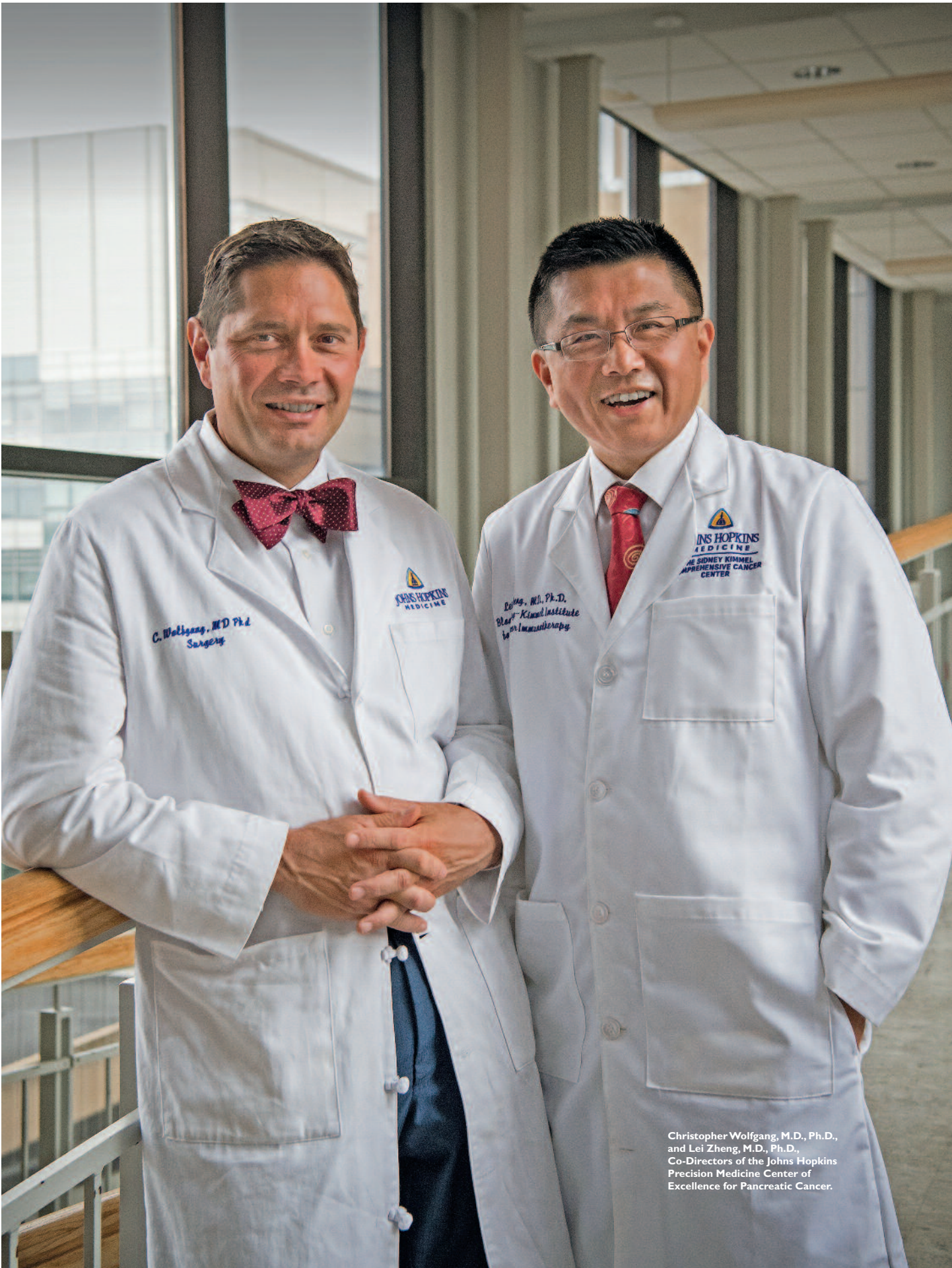
THE JOHNS HOPKINS KIMMEL CANCER CENTER

PANCREATIC CANCER MATTERS



PRECISION MEDICINE

THE RIGHT TREATMENTS.
TO THE RIGHT PATIENTS.
AT THE RIGHT TIME.



Christopher Wolfgang, M.D., Ph.D., and Lei Zheng, M.D., Ph.D., Co-Directors of the Johns Hopkins Precision Medicine Center of Excellence for Pancreatic Cancer.

PRECISELY!

Our new Precision Medicine Center of Excellence for Pancreatic Cancer gets the right treatments to the right patients at the right time.

LITTLE MORE THAN A YEAR since his diagnosis with pancreatic cancer that had spread to his liver, 68-year-old **Arnold Simon's** cancer is gone. This outcome is almost unheard of with any advanced cancer, let alone advanced pancreatic cancer, overall one of the deadliest types of cancer. Achieving these kinds of unprecedented results for patients is the mission of the new **Precision Medicine Center of Excellence for Pancreatic Cancer**, one of the first at Johns Hopkins.

It wasn't a coincidence that Simon beat the odds. A clinical trial developed by pancreatic cancer expert **Dung Le, M.D.**, testing a low-dose combination of five drugs—four that had already demonstrated an ability to attack pancreatic cancer cells and one that most considered ineffective for the cancer—was aimed at helping patients with advanced pancreatic cancer.

Le believed combining drugs that had shown some ability to kill pancreatic cancer cells would multiply the effect against the cancer. To make the drug combination an option for patients required some creativity. Each drug has its own toxicities, so combining the drugs at standard doses would multiply toxicities and be too harmful to patients, explains clinical research nurse manager **Katrina Purtell, R.N.**, who collaborates with Le on the multidrug trial funded by **Swim Across America**. Le decided to try the drugs at lower doses.

Le based her hunch on laboratory evidence that the power of the five drugs at lower doses would be greater than the higher doses of any one of the drugs alone. Simon has no doubt that he is a pancreatic cancer survivor because of Le's ingenuity. "No one else thought of putting these drugs together like this," he says.

This new trial, and many others aimed at improving pancreatic cancer survival, are derived from years of science, and the new Precision Medicine Center of Excellence is tasked with advancing this progress more quickly. The Precision Medicine Center is directed by **Christopher Wolfgang, M.D., Ph.D.**, one of the world's leading


pancreatic cancer surgeons, and clinician-scientist **Lei Zheng, M.D., Ph.D.**, who is developing novel strategies to prompt the immune system to attack pancreatic cancer.

"Our research has shown that most cancers will require multiple agents to alter or interfere with the multiple signals that drive cancers," says Zheng. "But what if we had an assay to predict the patients' response to one specific component or a combination of components among the five drugs we would be able to further lower the toxicity and treat the cancer more precisely. This is what precision medicine is all about. Getting patients just the right treatment—not too much and not too little."

Much of clinical cancer research has been based on giving patients the "highest tolerable dose" of anti-cancer drugs to kill as many cancer cells as possible. This approach has dominated clinical cancer research and drug discovery for decades, but Zheng and Wolfgang believe precision medicine is surely shifting this paradigm.



Arnold Simon

A portrait of Dung Le, M.D., a woman with long brown hair, smiling and wearing a white lab coat. The background is a soft, out-of-focus light blue.

“What makes a treatment work in one patient and not another is central to precision medicine and directing patients to therapies that will help them and away from ones that won’t.”

Dung Le, M.D.

Precision medicine-based, targeted therapies are more about reprogramming cancer cells to behave like normal cells by zeroing in on a specific defect or defects in cancer cells or cells supporting cancer’s growth and interfering with the cells’ ability to communicate cancer-promoting signals. This shifts away from the high-dose therapies that essentially blanket the body with poisons, killing cancer cells but also many normal cells. More recent research has shown that less can be more when it comes to these targeted cancer therapies. Le, Zheng, Wolfgang and colleagues are finding that some drugs work as well, or better, at lower doses, and these lower doses usually translate to less collateral damage to normal cells, which means fewer side effects for patients. In a disease such as cancer that has been defined as much by its life-threatening nature as the quality of life-altering side effects of its treatment (infection risk, nausea, hair loss, fatigue), this is huge progress.

Of the 50 patients Le has treated so far with the experimental drug combination, three others had responses similar to Simon and were able to have their pancreatic tumors surgically removed.

“This is not the type of outcomes we have seen in the past, but it’s exactly the direction we expect precision medicine approaches to take us,” says Wolfgang. Exciting new therapies that make inoperable pancreatic cancers operable offer opportunities to transform the trajectory of advanced pancreatic cancers.

Zheng and Wolfgang also want to understand what is different about the four cancers that converted from inoperable to operable and the varied response in the 46 other patients. “What makes a treatment work in one patient and not another is central to precision medicine and directing patients to therapies that will help them and away from ones that won’t,” says Zheng. “There is no one size fits all when it comes to cancer treatment.”

Le and collaborators will use precision medicine research models to go back to the laboratory to learn why patients like Simon had such dramatic responses while others did not. They will look for biomarkers, identifying characteristics within pancreatic cancer cells and other cells near and around tumors that can help differentiate responders from nonresponders.

“If we know a subset of pancreatic cancers act in a certain unique way,

we can look for a biomarker that represents this subset,” says pathologist **Robert Anders, M.D., Ph.D.** “Then, when new patients come in with the same marker, we’ll understand how that cancer is going to act and what treatment to give. We may even be able to figure out how to convert a different cancer to behave more like one that responds to treatment.”

In Simon’s case, Wolfgang believes it may be a mutation in a gene known as BRCA that gave the multidrug therapy an edge against his cancer.

Le added the drug cisplatin to her combination, a drug that is not typically used to treat pancreatic cancer. Recent research by Wolfgang found that platinum-based chemotherapy, like cisplatin, is linked to better survival rates in patients with BRCA1 or 2 mutations.

This latest finding builds upon an earlier discovery by **Scott Kern, M.D.**, an expert in genetic alterations in pancreatic cancer, and **Ralph Hruban, M.D.**, director of the Sol Goldman Pancreatic Cancer Research Center, that linked BRCA mutations to pancreatic cancer. Kern also showed that cancer cells containing BRCA mutations might be sensitive to cisplatin. Mutations to these

genes are often inherited and more common among people of Ashkenazi Jewish descent. The genetic alteration increases the risk of developing certain types of cancer, including pancreatic cancer. Simon is Jewish, and closer examination of his cancer showed it contained a BRCA mutation.

Precision medicine bridges the laboratory and clinic, often with targets for treatment identified from laboratory exploration of the inner workings of the pancreatic cancer cell being matched to available drugs that hit these targets. There is much back and forth as clinicians and scientists work together to identify cancer's vulnerabilities and develop therapies that exploit them.

"The interconnectivity of the laboratory and clinic to allow the quick translation of research findings to clinical care is a key characteristic of precision medicine," says Wolfgang.

THE PATH TO PRECISION

Decades of research and advanced technologies have gotten us to this point. They provide a new vantage point that affords scientists the ability to isolate and explore all components of cancer cells and the supporting cast of cells—the genetic hardware and the chemical software—to uncover the culprits that drive pancreatic cancers and expose vulnerabilities that can inform new treatments. These drivers include gene mutations or physical changes to the instruction manual that tell cells how to behave, epigenetic alterations or chemical changes to the DNA that also alter cell behavior, cancer's ability to evade the immune system and the immune system's willingness to tolerate cancer, and an entire micro-society around tumors that can cause cancer-inciting inflammation or help provide nutrients and other products essential to cancer cell survival. Each of these guides the treatment plan and is the basis of precision medicine approaches.

"We are tailoring what we do based on the biology of the tumor, but there is much more to this than technology and information. It's also



MANAGING SIDE EFFECTS OF IMMUNOTHERAPY

A Conversation with Jarushka Naidoo, M.B.B.Ch.

Immunotherapy is a promising new therapy that activates the immune system to attack cancer cells.

It has a completely different side effect profile than chemotherapy, and that has caught some physicians off guard. Doctors—including emergency room physicians, dermatologists and gastroenterologists—need to learn about immunotherapy.

What do patients and doctors need to know about immunotherapy side effects?

The Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy is leading the way and setting national standards for recognizing and managing immunotherapy side effects. These side effects can present with a wide range of symptoms, so their management requires the cooperation of many experts. We have assembled a group of specialists in ebody that has the potential for adverse reactions to immunotherapy, and they are on call for us 24/7. It is important for doctors and patients to call right away if they experience any symptoms, even if they believe them to be minor.

How are you educating patients about immunotherapy side effects?

Our patients come from all over the country. They could end up in emergency rooms or offices with doctors who do not understand patients' symptoms or mistake them for infections and provide incorrect treatment with devastating consequences. To prevent this, all our immunotherapy patients are given a wallet card to carry with them at all times to share with any doctor they see. The card says, "I'm on immunotherapy. Please contact my oncologist." The card provides contact information and the name of the drug or drugs patients are on. We also have a patient hotline, pager and email system.

What about doctors?

I am attending national cancer meetings with a Bloomberg~Kimmel Institute nurse to educate other doctors and working with organizations such as the National Comprehensive Cancer Network to share what we have learned and to establish standards for managing immunotherapy side effects. We are also working on a web-based course for doctors.

Lei Zheng, M.D., Ph.D., and
Christopher Wolfgang, M.D., Ph.D.



our multispecialty collaboration that allows us to move beyond simply accumulating information to using it wisely to make a difference for patients,” says Zheng. “We have the expertise to understand what things are actually driving the cancer so that we can match available drugs to actionable targets. This is essential because attacking a target that is not influencing a cancer is not of much use and can actually be damaging.”

Sophisticated computer databases help marry the laboratory data to the human data, taking into account treatment outcomes, side effects, length of response, recurrences and other survival trends to arrive at the most effective and least toxic therapies.

“Our experts are uniquely positioned to make progress because much of the science that inspired precision medicine unfolded here,” says Zheng.

In 2008, Kimmel Cancer Center

experts completed the genetic blueprint for pancreatic cancer, mapping out all the mutations in known human genes linked to cancer that make proteins that tell cells how to behave. The discovery uncovered an unexpected terrain of diversity in alterations from tumor to tumor. It explained why seemingly similar cancers often responded very differently to the same treatments. Still among the diversity were also some commonalities. Most of the mutations occurred in the same gene pathways, connected interactions that may conspire to promote cancer.

“This was the launching point for precision medicine,” says Wolfgang. “We could now use genetics to guide treatment and measure its effectiveness. We could drill down to the molecular level to look for alterations to target with drugs and determine if microscopic cancer cells, invisible

in imaging, remained after surgery that could seed a recurrence without additional treatment.”

With the genetic blueprint of pancreatic cancer complete, other researchers could begin to probe deeper and create a more complete picture of pancreatic cancer from origin to metastasis. This work expands opportunities to earlier detection and possibly, one day, prevention.

CLUES INSIDE THE CELL

Alison Klein, Ph.D., a researcher in the Sol Goldman Pancreatic Cancer Research Center, studies common gene variations that sometimes lead to



pancreatic cancer.

“Most people who have them will never develop pancreatic cancer, but studying these changes can help us

understand why some people develop the cancer,” says Klein. “Combining this information with other data we have on pancreatic cancer may help us figure out who is most at risk.”

Although Le’s multidrug treatment shows the promise to convert inoperable pancreatic cancers to operable, Wolfgang hopes precision medicine may also lead to earlier detection, before the cancer has spread. He and Klein are part of a team that developed a blood test that spots tumor-specific DNA and protein biomarkers of early-stage pancreatic cancer. Tumors tend to shed their mutated DNA into the bloodstream, making it possible for scientists to use gene-sequencing technology to sift through the blood and fish out DNA molecules specific for cancer amid a wide sea of normal DNA circulating in the blood.

Wolfgang also helped develop a gene-based test that distinguishes harmless pancreatic cysts from cysts that are likely to become cancer.

Elizabeth Jaffee, Daniel Laheru and Beth Onners hosted long-term pancreatic cancer survivors, providing tours of the laboratory where the treatments that saved their lives were invented.

These fluid-filled cysts are found in more than 1 million patients each year who have undergone CT or MRI scans because of abdominal pain and swelling. Imaging and even examining the fluid inside the cysts does not provide precise markers for precancerous potential, he says.

“The combination of genetic tests and clinical evaluation of patients’ cysts may change the way we guide patients on whether surgery to remove cysts is necessary,” says Wolfgang. “A panel of genetic markers, combined with clinical expertise, can accurately differentiate among types of pancreatic cysts and identify cysts that are safe to watch over time and cysts that need to be removed.”

Wolfgang, who leads one of the busiest pancreatic surgery programs in the world, credits his patients with helping pioneer these types of pancreatic cancer precision medicine approaches. “They have willingly provided the tumor samples scientists studied to identify the molecular changes that cause pancreatic cancers to form and grow,” he says.

THE SKIP VIRAGH CENTER

This convergence of science, technology and clinical care that is accelerating progress against pancreatic cancer patients is rooted in the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. It is the model for multispecialty care, as one of the first to bring all the experts together to offer newly diagnosed patients a comprehensive consultation involving all the specialists contributing to the treatment and diagnosis of pancreatic cancer. Patients and experts partner to come up with the best treatment approach.

“I don’t think there is another place in the world set up to provide this kind of care,” says **Daniel Laheru, M.D.**, co-director of the Skip Viragh Center. “Every patient who comes to us receives individualized care. For some, treatments are based on molecular markers from the onset. Other patients may receive standard of care, and if the treatment stops working or the cancer comes back, we can use molecular testing, imaging and all available tools to devise a new approach.”



Sitting from left; Florence Campi, John Dowell, Kathleen Dowell
Standing from left; Elizabeth Jaffee, M.D., Morris Campi, Daniel Laheru, M.D., Beth Onners, R.N., Chuck Bender, Donna Bender, Joan Rodriguez, Manuel Rodriguez



Daniel LaHeru, M.D., and patient Nancy Azzaro

More than 40 physicians, surgeons, research nurses and other staff members dedicated to pancreatic cancer make up the Skip Viragh Center. “We are making unheard-of progress in diagnosis, staging, research and individualized care,” says **Elizabeth Jaffee, M.D.**, co-director of the Skip Viragh Center. “Everything that can be done for pancreatic cancer is being done in our Skip Viragh Center and Precision Medicine Center of Excellence for Pancreatic Cancer, and we are sharing with others so that our concepts can be used to help pancreatic cancer patients everywhere.”

PRECISION IN PRACTICE

Gene Ogle is among these patients. When he was diagnosed with



pancreatic cancer at age 54, his first question was, “How long do I have to live?” His father died 30 years earlier of the same disease.

“My father died two months after he was diagnosed. My knowledge

was that it was incurable and killed quickly,” says Ogle.

The multidisciplinary team of experts recommended surgery, specifically the Whipple procedure, a complex pancreatic cancer surgery refined by **John Cameron, M.D.**, Wolfgang and other Johns Hopkins surgeons.

They also told him about a clinical trial studying a pancreatic cancer vaccine developed by Jaffee that could be administered in the weeks leading up to surgery. The goal of the vaccine is to attract cancer-killing immune cells to the tumor to prevent the cancer from coming back after surgery. The trial, led by Zheng, was aimed at decreasing the high rate of cancer recurrence caused when microscopic cancer cells break away from the tumor and travel through the bloodstream to other parts of the body. The vaccine would teach the immune cells to recognize pancreatic cancer cells and go after them wherever they are located in the body.

“Enrolling in the vaccine trial was an easy decision for me, and I have never regretted it one time,” says Ogle, who adds that he still didn’t have much hope for long-term survival.

Seven years, a 60th birthday cele-

bration and two grandchildren later, he says: “My perspective is changing. I am so thankful that I lived to see these things. I didn’t think I would, but I’m beating this disease, and that’s a message people need to hear.”

He’s not the only one. The Skip Viragh Center recently hosted a luncheon for other long-term survivors and their families. In many ways, these patients are the founders of precision medicine. Their experiences are guideposts, as researchers and clinicians work together to reveal the cellular reasons for their remarkable responses. They provide real-life testimony to why Johns Hopkins leadership selected pancreatic cancer as a Precision Medicine Center of Excellence. These types of unprecedented success stories are the result of collaborative laboratory and clinical research, and demonstrate what is possible when innovative science, medicine and technology are connected.

Kathleen Dowell, Donna Bender, Morris Campi and Manuel Rodriguez are members of an exclusive club—pancreatic cancer patients who have defied the odds. Blood and tumor samples they provided during their treatment are helping our experts understand why and how, and have led to precision medicine approaches being studied today. For Zheng and Wolfgang, these patients are living proof that curing pancreatic cancer is possible.

“The goal of the Precision Medicine Center of Excellence for Pancreatic Cancer is to make these kinds of outcomes the norm,” says Zheng.

The group toured Jaffee’s lab and saw firsthand how their blood and tissue samples are used in research, and how this research is improving treatments for pancreatic cancer patients today.

Dowell, who was diagnosed in 1997, recalled recovering from her Whipple surgery and thinking about the grim survival statistics for pancreatic cancer patients when she learned about the vaccine. She received just two in-

jections, the fewest of anyone on the study, but had the most significant immune response.

Rodriguez, like Dowell, received Jaffee's vaccine and is also a 20-plus year survivor. He came to the Kimmel Cancer Center after a surgeon at the community hospital near his Florida home told him that he had no chance of survival. Blood samples he provided revealed a unique enzyme that may offer clues to his response and could also benefit other pancreatic cancer patients.

Bender, too, sought out the Kimmel Cancer Center, when doctors told her that, at best, she had a few years. Now, 16 years later, she was thrilled to spend time with the inventor of the vaccine where all the research was done.

"I always wanted to meet Dr. Jaffee," says Bender. "She is my Wizard of Oz, doing something magical behind a curtain."

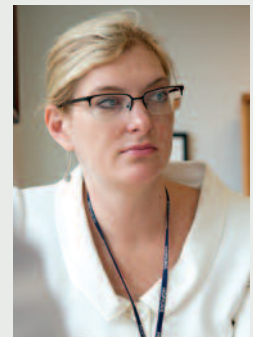
Campi was told he probably had between a 2 and 5 percent chance of surviving. Now, 14 years later, the 85-year-old, who was treated with surgery, radiation therapy, chemotherapy and 10 years of vaccine therapy, has no signs of pancreatic cancer. He goes to the gym regularly and says he feels "pretty good."

Dowell's two injections versus Campi's 10 years of therapy are providing precious information that is helping researchers determine what types and combinations of therapies work and in whom, when to give them, and how long to give them.

"This is what precision medicine is about—putting all of these puzzle pieces together to create better therapies for patients," says Zheng, who collaborates with Jaffee on new, better-working versions of the vaccine that exploit molecular clues uncovered through patient-provided blood and tissue samples. "We have leaders in surgery, immunotherapy, pathology, genetics and epigenetics research. New discoveries are being made as a result."

PATHOLOGY AND PRECISION MEDICINE

A Conversation with Robert Anders, M.D., Ph.D., and Janis Taube, M.D.



What is the role of pathology in cancer immunology?

Pathologists look at what's going on in and around tumor cells to see the numbers and kinds of cells that are present, including immune cells. Tests, called assays, find biomarkers that alert us to the presence of particular proteins, mutations and other characteristics that can predict an immune response or point at things that are getting in the way of the immune response.

How does pathology research improve immunotherapy?

Pathology played a key role in two recent discoveries that led to FDA approvals and changed the standard of care. The genetic defect, called mismatch repair deficiency, or MMRd, is now one of the most important biomarkers of immune response. If a pathologist sees this defect in a cancer, regardless of the cancer type, that patient now receives anti-PD-1 immunotherapy as a firstline treatment. PD-L1 expression is another biomarker that identifies cancer patients who are more likely to respond to immunotherapy.

"Immunotherapy is one of the most promising new cancer treatments, and we think we can make it work in more patients by combining immunotherapies."

What are you most excited about?

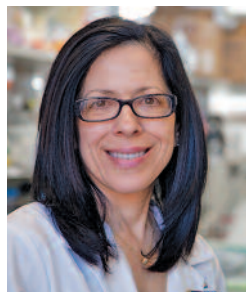
Immunotherapy is one of the most promising new cancer treatments, and we think we can make it work in more patients by combining immunotherapies. Pathology is key to guiding these combinations. We are already combining two immunotherapies using drugs that block two different immune checkpoints that interfere with the immune response against cancer; and soon we expect to be introducing clinical trials using three immunotherapies. We continue to look for and uncover additional characteristics that identify cancers that will be vulnerable to immunotherapy.

THE IMMUNE COMPONENT

Jaffee, a leader in cancer immunology, is excited about promising new approaches that, like her vaccine, make the immune system recognize and attack pancreatic cancer.

“Immunotherapy is a form of precision medicine because each time we give a treatment, it’s not acting in the same way in each patient. It’s acting on that particular patient’s immune system,” says Jaffee. “How the immune system sees the cancer is unique in each patient.”

Jaffee, who is an associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy, says



Kimmel Cancer Center experts are leading the way, unraveling the science that led to her immune-

boosting pancreatic cancer vaccine and new immunotherapy drugs. With precision medicine in mind, they are developing biomarker tests that identify patients likely to benefit from immunotherapy and developing new ways to convert immune-resistant cancers to immune-responsive cancers.

Two new drugs called pembrolizumab (Keytruda) and nivolumab (Opdivo) are among a class of immunotherapies known as checkpoint inhibitors that release a brake cancer cells put on the immune response, allowing the immune system to do its job and attack cancer cells. The drugs work particularly well in cancers that contain a spell-checklike failure in their DNA called mismatch repair deficiency. This failure allows DNA errors to go uncorrected, initiating an accumulation of gene mutations and contributing to the development of many different types of cancer, including pancreatic cancer. The large numbers of mutations caused by mismatch repair deficiency make cancer cells look different from normal cells. Immune cells recognize

this difference, much like they recognize foreign invaders, such as bacteria and viruses.

Le led a clinical trial testing pembrolizumab in patients with mismatch repair deficiency. The work led to FDA approval of the drug for any patient whose cancer contains this genetic repair defect, regardless of type or stage. It is the first time a cancer drug has been approved based on a specific genetic profile instead of a cancer type. This type of shift is at the core of precision medicine, where studies of new drugs are no longer in all patients with late-stage or aggressive cancers that do not respond to standard treatments. Instead, using biomarker tests, our doctors can identify patients whose cancers have the unique characteristics that portend a likely response to a drug and get the optimal therapy to patients upfront.

“Potentially, we could customize what drugs we combine with the vaccine at an individual level.”

“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. Given the potential for durable clinical benefit, we now have a reason to test for DNA mismatch repair deficiency in almost any cancer,” says Le.

The mismatch repair deficiency finding led Jaffee and two other Skip Viragh Center researchers, **Mark Yarchoan, M.D.**, and **Alexander Hopkins, Ph.D.**, to take another look at gene mutations and explore exactly how big an effect the number of mutations has on response to immune checkpoint inhibitors across many different cancer types. They analyzed more than 27 cancer types and found that mutational burden, or the number of gene mutations a cancer has, is the single most significant predictor of response to immunotherapy with checkpoint inhibitors.

“More than half of the differences in how well cancers responded to immune checkpoint inhibitors could be explained by the mutational burden of that cancer,” says Yarchoan.

Tumor mutations, typically viewed as the defining characteristic of the cancer cell because they cause a normal cell to turn malignant—giving it the ability to survive, grow and spread—are actually beneficial when it comes to immunotherapy.

“The idea that a tumor type with more mutations might be easier to treat than one with fewer sounds a little counterintuitive. It’s one of those things that doesn’t sound right when you hear it,” says Hopkins. “But with immunotherapy, the more mutations you have, the more chances the immune system has to recognize the tumor.”

Jaffee, Yarchoan and Hopkins developed a computerized tool that calculates mutational burden to predict individual tumors most likely to respond to immunotherapy. Future studies might also focus on finding ways to prompt cancers with low mutational burdens to behave like those with higher mutational burdens so that they will respond better to these therapies.

“This is precision medicine—moving beyond what’s true for big groups of patients to see whether we can use information to help any given patient,” says Yarchoan.

Yarchoan, Le, Zheng and others are collaborating with Jaffee to use checkpoint inhibitors to augment the immune-boosting effect of her pancreatic cancer vaccine. The vaccine improves the immune response, recruiting many cancer-attacking T cells to the tumor site only to be signaled by cancer cells to stop.

Combining the vaccine with checkpoint inhibitors, and potentially other immune cell-stimulating drugs, may remove brakes on the immune response to the cancer.

Wolfgang is excited about mounting evidence coming from these clinical trials that shows giving a checkpoint inhibitor or vaccine and checkpoint inhibitor before surgery decreases the size of tumors and keeps cancers from returning.

Some cancers naturally attract the attention of cancer-killing T cells, but pancreatic cancer typically is not one of them.

“The vaccine is the first step in turning pancreatic cancer into an immune-responsive cancer. Once it gets T cells into the cancer, we can help them do their work by removing as many restraints as possible,” says Yarchoan.

Jaffee and Yarchoan believe the immune checkpoints cancer cells exploit to stop T cells from doing their job may vary among patients. “Potentially, we could customize what drugs we combine with the vaccine at an individual level,” says Yarchoan.

Jaffee has leveraged their pioneering pancreatic cancer research nationally. Since 2014, she has led a Stand Up To Cancer-Lustgarten Foundation pancreatic cancer Dream Team focused on developing new immunotherapies. Of the 22 Dream Teams, this is the only one that is female-led, and with Jaffee at the helm, top pancreatic cancers experts from 11 cancer centers are engaged in the collaboration, resulting in five new clinical trials and more than 600 patients treated.

“Pancreatic cancer patients are looking for hope. Precision medicine is that hope.”

MOVING FORWARD

Simon, the patient who received Le’s multidrug regimen, still marvels at how quickly his doctors moved to help him. “They have a sense of urgency. I didn’t get that sense at other



Mark Yarchoan, M.D., Alexander Hopkins, Ph.D., and Elizabeth Jaffee, M.D., developed a computerized tool that calculates the number of mutations in a tumor, a biomarker that can predict response to immunotherapy.

hospitals,” says Simon. “I saw a surgeon on a Friday, had an appointment with Dr. Le the next Monday and began the trial two weeks later.”

Simon’s experience gets to the very heart of precision medicine. “I felt my health was more important to Dr. Le than her clinical trial and its results,” he says. “What was best for me was most important to her.”

Now, two years since receiving a dismal diagnosis of metastatic pancreatic cancer, Simon, a self-described “grumpy old Jewish guy,” is seeing things in a more positive light. Based on Le’s recommendation, he is now

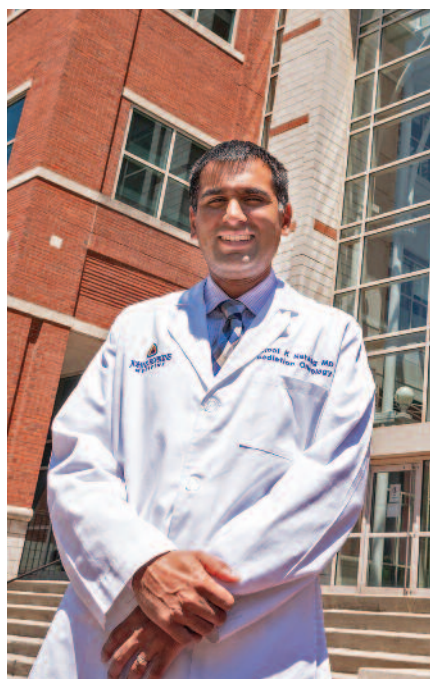
participating in another clinical trial for patients with inactive metastatic pancreatic cancer like his. The new treatment, as Simon describes it, “gets those lurking, hiding little cancer cells and zaps them before they get started.” The 68-year-old, who enjoys flying kites and bird-watching, is experiencing firsthand the power of precision medicine, and there is nothing more personal than that. He wears a hat emblazoned with a large button that says, “Attitude is everything.” The button was a gift from a friend and fellow cancer survivor. He says it reflects his new positive outlook.

Jaffee gets it. “Pancreatic cancer patients are looking for hope,” she says. “Precision medicine is that hope.” ●

Contact our Precision Medicine Center of Excellence for Pancreatic Cancer at 410-933-PANC (7262).

RADIATION THERAPY

Making Inoperable Cancers Operable



Amol Narang, M.D.

Three techniques—one that delivers external beam radiation more precisely, one that separates key normal organs away from tumors in order to protect the organs, and one that delivers radioactive treatments directly to tumors—are among new approaches radiation oncologist **Amol Narang, M.D.**, is using to improve pancreatic cancer survival.

Which technique is right for each patient is a matter of precision medicine and a key component of the Multidisciplinary Clinic in the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. All of the experts involved in the treatment of pancreatic cancer analyze all available information and partner with patients to recommend a treatment plan best suited to the unique characteristics of each patient's cancer. Narang's focus is using advanced

technologies and discoveries to help deliver higher doses of radiation more precisely to pancreatic cancers, allowing surgeons to successfully remove more and more cancers that were previously thought to be inoperable, which is necessary for patients to have a chance to be cured.

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

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

making surgery possible for more patients.

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

There is also evidence that high doses of radiotherapy may make cancer cells more responsive to subsequent treatment with immunotherapy. Radiation damage to the tumor may make it more recognizable to the immune system and may prime patients to respond better to new drugs that give the immune system an upper hand on cancer. The potential of this immune-boosting component in pancreatic cancer is the focus of clinical trials being led by **Lei Zheng, M.D., Ph.D.**, co-director of the Precision Medicine Center of Excellence for Pancreatic Cancer.

Narang is also studying a new material, known as hydrogel, that could make even higher doses of radiation

Advanced technologies and discoveries help deliver higher doses of radiation more precisely to pancreatic cancers, allowing surgeons to successfully remove more and more cancers that were previously thought to be inoperable.

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

therapy possible for pancreatic cancer. The risk of harming the bowel, which is one of the most sensitive organs in the body to radiation, currently limits the dose of radiation that can be given, Narang says. This new product may solve that problem.

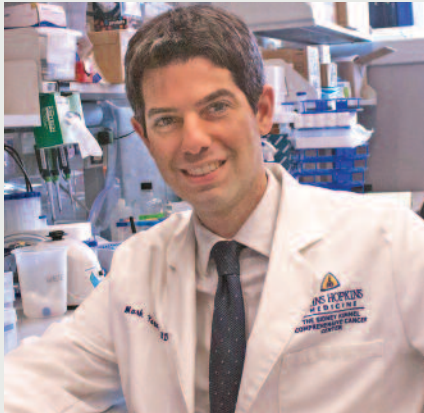
"The pancreas is surrounded by bowel, but if we can inject hydrogel to increase the distance between the pancreas and the bowel, we may be able to deliver higher doses of radiation to the pancreas without harming the bowel," says Narang. ●

PRECISION MEDICINE

In Action

GETTING BETTER RESULTS FOR GI CANCER PATIENTS

Mark Yarchoan, M.D., is actively pursuing several ways to make immunotherapy work better for patients with gastrointestinal cancers, including pancreatic, colon, liver and bile duct cancers.



“Immunotherapy has not worked as well in GI cancers as some other cancers, and we want to study new ways to make them more sensitive to immunotherapy treatments,” says Yarchoan.

Yarchoan and colleagues are exploring several approaches, including the use of vaccines to attract the immune system to the tumor. The vaccine is combined with a checkpoint inhibitor to prevent the immune cells that are stimulated by the vaccine from shutting down once they reach the tumor. An added aspect to this research is the development of new types of vaccines that may do a better job of rousing an immune response.

“There are two parts to vaccines. One part tells immune cells what to attack, and the other stimulates the immune system,” says Yarchoan. “Most cancer treatment vaccines have used GMCSE, a protein secreted by immune cells, to incite an immune response. We are trying to develop a new kind of adjuvant that works quite differently to maximally stimulate the immune system.”

He and Skip Viragh Center co-director, **Daniel Laheru, M.D.**, are collaborating on a study that uses a pancreatic cancer vaccine and the anti-PD-1 drug nivolumab before surgery to see if it can generate an immune response to shrink tumors and make them more amenable to surgical removal and less likely to recur. This study is funded by Fran and Jim McGlothlin.

Yarchoan is collaborating with Precision Medicine Center of Excellence Co-Director **Lei Zheng, M.D., Ph.D.**, and colon cancer expert **Nilo Azad, M.D.**, on a novel approach to make colon cancer more responsive to immunotherapy. The work builds upon an earlier discovery by Skip Viragh Center clinician-scientist **Dung Le, M.D.**, that linked a cancer cell defect known as mismatch repair deficiency to response to the immunotherapy drug pembrolizumab. They are exploring whether a cancer vaccine that stimulates the immune system can convert non-mismatch repair deficient colon cancers that are currently not responsive to pembrolizumab to immunotherapy responders.

“There are two parts to vaccines. One part tells immune cells what to attack, and the other stimulates the immune system.”

In bile duct cancer, he and Azad are leading a national clinical trial through the National Cancer Institute’s Cancer Therapy Evaluation Program to study the combination of the MEK inhibitor cobimetinib with the PD-L1 immune checkpoint inhibitor atezolizumab. It is the first clinical trial for bile duct cancer patients whose cancers come back following chemotherapy.

ACTION
Using a pancreatic cancer vaccine and the anti-PD-1 drug nivolumab before surgery, Yarchoan hopes to see if he can generate an immune response to shrink tumors and make them more amenable to surgical removal.

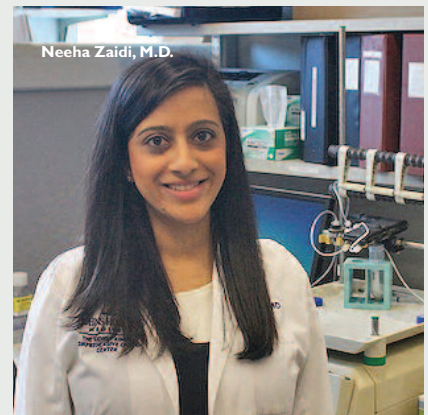
“We want to see if cobimetinib combined with atezolizumab works better than atezolizumab alone,” says Yarchoan. “There is currently no effective treatment for patients who progress after chemotherapy, and survival for these patients is unfortunately often measured in months,” says Yarchoan.

In liver cancer, he has started the first clinical trial of an immune checkpoint inhibitor before surgery. The trial uses an immune checkpoint inhibitor plus another drug called cabozantinib to try to shrink liver cancers before surgery and hopefully improve the chances of a successful and curative surgery. Yarchoan believes that cabozantinib may change the tumor to be more responsive to the immune checkpoint inhibitor while also helping to eliminate micrometastases, microscopic cells that can seed the spread of cancer.

“We hope this will improve the chance of cure,” says Yarchoan, who is collaborating with Laheru to also see if cabozantinib alters the cellular environment of tumors to improve the activity of nivolumab. ●

TARGETED VACCINES

Certain antigens can help the immune system distinguish cancer cells from normal cells. Neoantigens are proteins or signals from mutated cancer genes within a tumor that are unique to each patient’s cancer and, with a little help, can be recognized by the immune system.



Neeha Zaidi, M.D., is working on neoantigen-targeted vaccines for pancreatic and colon cancers. Using

Katie Bever, M.D.,
and patient Sandra Myers



a pancreatic cancer model, she and her collaborators have identified the most immunogenic neoantigens—the ones that attract the greatest numbers of cancer-attacking immune T cells to the tumor. The current version of the vaccine includes 12 neoantigens, but Zaidi says additional ones could be added.

A clinical trial that combines neoantigen-targeted vaccines with two other immunotherapy drugs, known as checkpoint inhibitors, is planned. While the vaccine draws immune cells to the tumor, the drugs release important brakes on the immune response. One drug will target and block PD-1, an immune

“stop” signal exploited by cancer cells, and the other interferes with an immune signal called OX40 to stimulate production of more immune T cells.

attention of the immune system and, with the addition of a checkpoint inhibitor, they respond well to immunotherapy. Zaidi believes the

“Our goal is to make more cancers respond to immunotherapy by making their mutations visible to the immune system.”

This approach builds on another Skip Viragh Center discovery, showing that cancers with a defect known as mismatch repair deficiency (MMRd) accumulate large numbers of mutations that serve as red flags for the immune system. Cancers with MMRd tend to draw the

vaccine/drug combination can make cancers that don't have the defect look like MMRd cancers and generate an immune response to the cancer.

“Our goal is to make more cancers respond to immunotherapy by making their mutations visible to the immune system,” says Zaidi. ●

ACTION
Zaidi is developing vaccines that draw immune cells to a tumor. The drugs stimulate the production of more immune T cells and release important brakes on the immune response.

CLINICAL TRIALS FOR TREATMENT-RESISTANT CANCERS

Katherine Bever, M.D., is collaborating with Dung Le, M.D., on a clinical trial for patients with advanced pancreatic cancers that have spread outside the pancreas. The trial combines a pancreatic cancer vaccine to bring cancer-killing T cells to pancreatic tumors with drugs that block two immune checkpoints, called PD-1 and IDO, that cancer cells hijack to shut down the immune response. The combination therapy is followed by a listeria vaccine engineered to express mesothelin, an immune cell-alerting signal common to pancreatic cancer. The trial is designed for patients who did not respond to the pancreatic cancer vaccine and anti-PD-1 immunotherapy. Bever hopes the four-pronged approach will work synergistically to stimulate the immune system while also removing cancer-imposed brakes on the immune response.

With funding from **Swim Across America**, Bever has also begun research of high-grade neuroendocrine tumors, a very aggressive type of pancreatic cancer that often responds poorly to treatment. She will be exploring the microenvironment, the cellular environment in which the tumor lives, for clues that could lead to ways to make these tumors respond to immunotherapy with checkpoint inhibitors. ●

EXTENDING PROGRESS TO OTHER CANCERS

Evanthia Roussos Torres, M.D., Ph.D., is taking what she learned working in the lab of Elizabeth Jaffee, M.D., to help patients with breast cancer, but the precision medicine model she is developing for HER2-positive breast cancer can also be applied to pancreatic cancer.

The research is aimed at converting nonimmunogenic tumors—ones that don't respond to immunotherapy—to immunogenic tumors—ones that respond well to immunotherapy.

HER2-positive breast cancer produces a cancer cell growth-stimulating



protein known as the human epidermal growth factor receptor 2. Therapies that target HER2, like the drug trastuzumab (Herceptin), have improved survival, but a significant number of breast cancer patients see their cancers return. Roussos Torres' approach involves using a combination of the immune checkpoint inhibitors ipilimumab and nivolumab with an epigenetic-targeted drug called etinostat. Checkpoint inhibitors release important brakes the cancer cell puts on the immune response, and the epigenetic drug changes the chemical environment of cells to make them more amenable to immunotherapy.

“Basically, we believe this treatment combination allows immune T cells to infiltrate tumor cells and to do a better job.”

“Basically, we believe this treatment combination allows immune T cells to infiltrate tumor cells and to do a better job,” says Roussos Torres.

Engaging the immune system to fight cancer has been shown to prevent cancers from coming back, resulting in long-lasting responses in several tumor types. In the laboratory, Roussos Torres has zeroed in on about a half-

dozen genes that can be epigenetically targeted to decrease immune suppression. Although etinostat broadly hits many genes, she is working to tease out certain genes to develop a precision approach that only hits genes that are specific to improving the response to anticancer therapies.

“We think there may be interplay between the trastuzumab (Herceptin) signaling pathway and immune checkpoint inhibition occurring through etinostat,” she says. “We need to flesh that out so we can understand how these signaling pathways are talking to one another to get the desired response.”

She is collaborating with breast cancer expert **Roisin Connolly, M.B.B.Ch.**, to evaluate the combination therapy in patients.



“In a clinical trial, we will be able to isolate responders from nonresponders and compare what we see to laboratory models to better understand the mechanisms,” says Roussos Torres. This will allow them to identify biomarkers that will help guide the therapy to those patients most likely to benefit. ●

CANCER VERSUS THE IMMUNE SYSTEM

Immunotherapy works extraordinarily well in a subset of cancer patients—sometimes making what were thought to be incurable cancers curable. However, it doesn't work in all patients. **Tara Robinson, M.D., Ph.D.**, is focused on understanding why this promising new cancer treatment works so well in some patients and

PRECISION MEDICINE **In Action**

not in others. What she learns may lead to precision medicine approaches that make immunotherapy more effective and an option for more patients.

Robinson says a lot of effort has been placed on understanding the tumor, including the genetic changes that drive growth and drugs that can target these genetic changes. For her research, she has chosen a different path, looking instead at what cancer cells—and the treatments we use to combat them—do to the immune system.

“I want to know how cancer and cancer therapy change the immune system to find new opportunities to improve treatment responses,” she says.

chemotherapy,” says Robinson. She wonders if previous treatment with chemotherapy could be dampening the immune response in some patients.

“When we talk about immunotherapy, we compare the immune system to a car and use an analogy of releasing the brakes to get the car, aka the immune system, moving, but what if your car is totaled? Releasing the brakes really won’t be much help,” she says.

The science of immunology, and technologies available to researchers, has improved dramatically since that 1990s breast cancer study was published, and Robinson is using a mouse

some point. We need to know what it’s doing to the immune system.”

Ultimately, she hopes to use her findings to help guide immunotherapy based on the type of chemotherapy patients have received.

“The impact on immune cells may be different for patients who have never had chemotherapy or have received one type of chemotherapy versus another. Different chemotherapy drugs may have varying effects on immune cells. Understanding these differences can tell us what types of immunotherapy are likely to work in a patient and what approaches may not work,” says Robinson.

“This is personalized treatment based on immune parameters rather than tumor parameters.” ●

FINDING THE RIGHT COMBINATION

May Tun Saung, M.D., is conducting several clinical studies building upon



May Tun Saung, M.D.

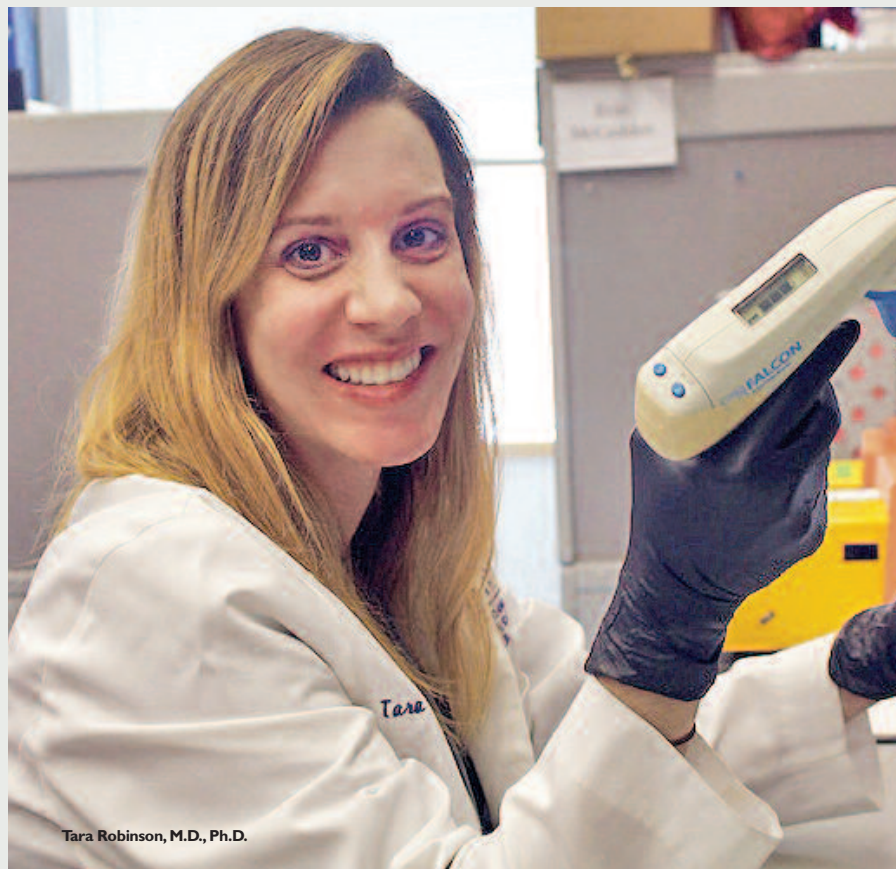
laboratory research that showed adding a macrophage-modifying drug to a pancreatic cancer vaccine and anti-PD-1

checkpoint inhibitor combination may improve the immune response to pancreatic cancer.

Macrophages are a type of white blood cell that play a critical role in the body’s immune response but are corrupted by cancer cells to help the tumor instead of destroying it.

Saung’s approach uses the vaccine to draw cancer-killing immune cells to the tumor and an anti-PD-1 checkpoint inhibitor and a macrophage-targeted drug to convert immune suppressing signals to immune-activating signals.

In pancreatic cancer animal models, immune T cell activation went up and survival was extended when the macrophage-targeted drug was added to the vaccine and anti-PD-1 drug combination. Saung is working to translate these laboratory findings to patients. ●



Tara Robinson, M.D., Ph.D.

A breast cancer study from the 1990s that showed chemotherapy had a long-lasting impact on immune cells, with T cells and B cells taking up to two years to return to normal function, led her to explore the effect of chemotherapy on each type of immune cell.

“Immunotherapy has become a first-line treatment for some cancers, but in general, we use it when a patient’s cancer does not respond to traditional

model of pancreatic cancer to precisely measure the effect of chemotherapy on subsets of immune cells, including cells that suppress immune activity.

“When a tumor is established and growing and the patient gets chemotherapy, how does that change the game? This is an area that is underinvestigated,” she says. “Even with the predicted growth in immunotherapy, most cancer patients will still receive chemotherapy at

IN THE NEWS



Elizabeth Jaffee, M.D., and Mark Yarchoan, M.D., discuss breaking research at AACR meeting.

Elizabeth Jaffee Installed As President of AACR

On April 17, Elizabeth Jaffee, M.D., became president of the American Association for Cancer Research, the world's oldest and largest cancer science organization. Jaffee, an international leader in pancreatic cancer research and cancer immunology, is deputy director of the Kimmel Cancer Center, co-director of the Skip Viragh Center for Pancreatic Cancer Clinical Research and Patient Care, associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy, and the Dana and Albert "Cubby" Broccoli Professor of Oncology.

During her term as president, Jaffee says AACR will focus on:

- Cancer health disparities
- Cancer prevention, early detection, and interception
- Combination therapies and precision oncology (immunotherapy/radiation/targeted)
- Convergence science
- Hematologic malignancies
- Implementation and behavioral sciences
- Novel clinical trial designs
- Pathology
- Pediatric cancer
- Radiation science and medicine
- Survivorship research

Her goals include engaging engineers, mathematicians, physicists, computational biologists, chemists and experts in other relevant fields, such as artificial intelligence, to apply their expertise toward existing cancer problems.

"We are at an unprecedented time in history, when new treatments and technologies are rapidly reshaping patient care," says Jaffee. "Together we will prevent and cure all cancers through research, education, communication, and collaboration."

"We are at an unprecedented time in history, when new treatments and technologies are rapidly reshaping patient care."

Jaffee was also elected to the American Association for Cancer Research Academy. The academy recognizes and honors distinguished scientists whose major scientific contributions have propelled significant innovation and progress against cancer. Jaffee was honored for developing cancer vaccines and vaccine combinations that overcome tumor-associated immune tolerance.

These latest honors underscore Jaffee's extensive contributions to cancer research. She also serves as co-chair of the Cancer Moonshot Blue Ribbon Panel and its Immunology Working Group, and chair of the National Cancer Advisory Board. ●

IN THE NEWS



CLOCKWISE FROM TOP LEFT:
The Skip Viragh Outpatient Cancer Building; Mark Viragh, brother of Skip Viragh; Daniel Laheru, M.D.; Skip Viragh's siblings from left, Bob Viragh, Katherine Viragh, Jean Dahl, Mark Viragh; Close friend Roger Young views a mosaic, an artistic tribute to the Viragh family and people and programs dedicated to caring for patients and curing cancer; Elizabeth Jaffee, M.D., Mark Viragh, Daniel Laheru, M.D., Katherine Viragh. Attendees watched a video on the life of Skip Viragh.

Celebrating the Opening of Skip Viragh Outpatient Cancer Building

On June 8, 2018, approximately 200 people, including family, friends and business associates of Skip Viragh, Johns Hopkins leadership, donors and art committee members, celebrated Skip Viragh and the opening of the new outpatient cancer building that bears his name. The event was the culmination of Viragh's vision for a single place where cancer patients could have access to the best possible and most innovative cancer care.

Watch a video of the dedication event at bit.ly/2vshsDT

“Cancer is an unbelievable challenge. It’s tough, and that’s why Skip chose to give resources to it.”

Skip Viragh's siblings, daughters, grandchildren, companion, nieces and nephews were among the family members attending the dedication. Speakers honoring Viragh and marking the opening of the building were **Ronald Daniels**, president of The Johns Hopkins University; **Paul B. Rothman**, dean of the medical faculty; **Redonda Miller**, president of The Johns Hopkins Hospital; **William Nelson**, director of the Kimmel Cancer Center; **Daniel Laheru**, co-director of the Skip Viragh Center; **Mark Viragh**, Skip's brother; **Stacey Ullrich**, Under Armour representative; **Vered Stearns**, co-director of the Breast and Ovarian Cancer Program; and **Connie Viелlette**, a patient.

“Skip was one of the most influential and innovative people I have ever met,” said Laheru, who treated Viragh for advanced pancreatic cancer from his diagnosis in 2002 through 2004, when the disease claimed his life. “Skip and his family have helped so many people with pancreatic cancer and, with this building, all cancer patients. His name is a constant reminder to innovate and to never forget our core mission. Through the generosity of the Viragh family, his memory will endure forever as the heart of this building that will be a beacon of hope for patients and families for years to come.”

Skip Viragh's brother Mark spoke on behalf of the Viragh family, honoring Skip's pioneering spirit by donning his cowboy boots and hat. “Cancer is an unbelievable challenge. It's tough, and that's why Skip chose to give resources to it,” says Mark Viragh. “In partnering with Under Armour and getting others to come together to support this building, I know he has a smile on his face.”

Guests received guided tours of the 10-story building, which features 50 pieces of artwork—many of which were donated—selected by the volunteer art committee. ●

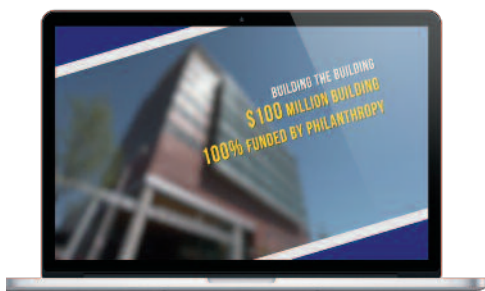
Take a video tour of the building at bit.ly/2MRSpxE



WEB EXCLUSIVE

Skip Viragh tribute - A Life Defined by Family, Friends and Philanthropy

Watch at bit.ly/2MriIxq



THE JOHNS HOPKINS KIMMEL CANCER CENTER

PANCREATIC CANCER MATTERS

A newsmagazine from the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care

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