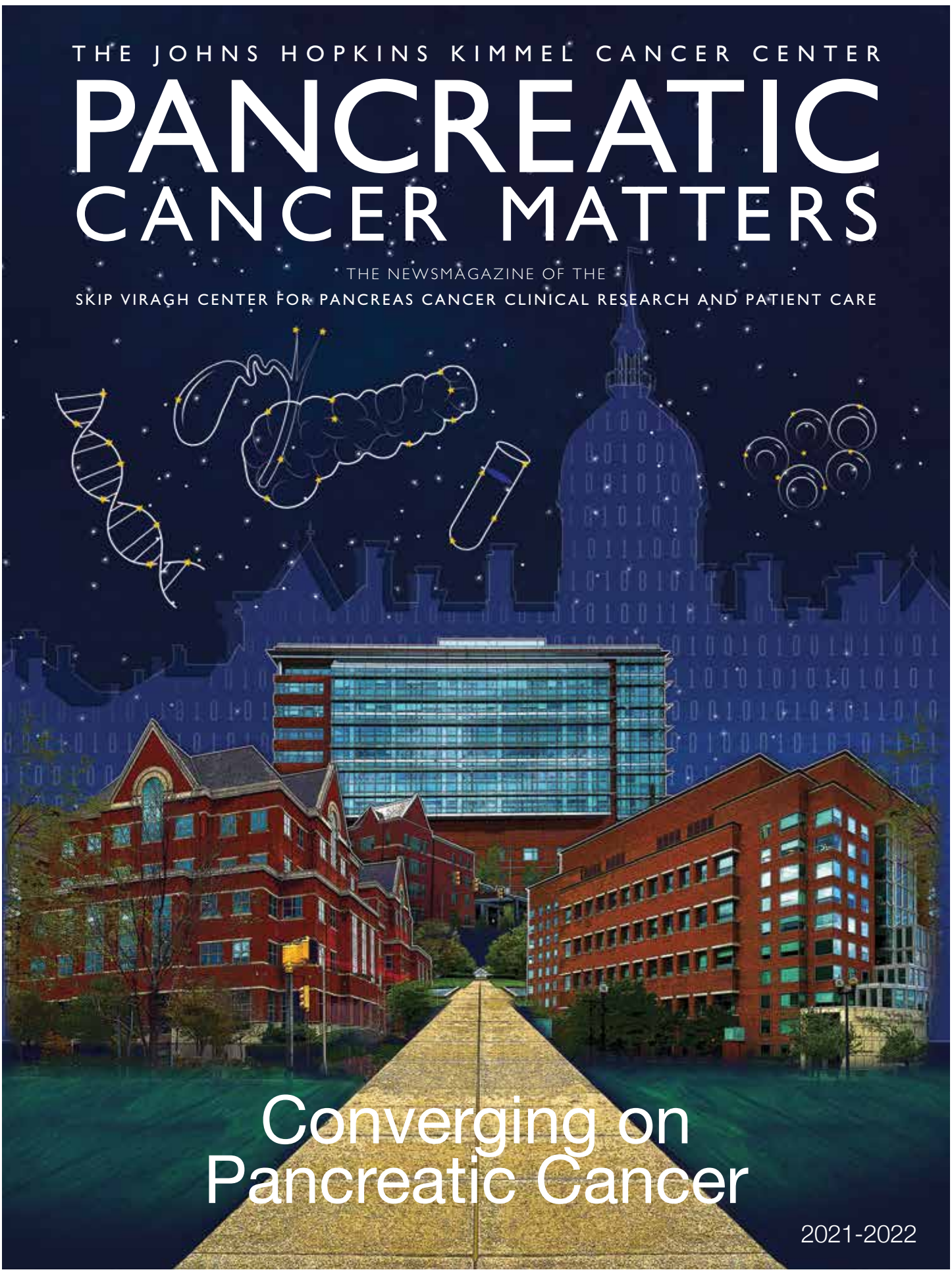
THE JOHNS HOPKINS KIMMEL CANCER CENTER

PANCREATIC CANCER MATTERS

THE NEWSMAGAZINE OF THE

SKIP VIRAGH CENTER FOR PANCREAS CANCER CLINICAL RESEARCH AND PATIENT CARE



Converging on Pancreatic Cancer

2021-2022

convergence INSTITUTE

CONVERGING ON PANCREATIC CANCER

The expertise and information to solve almost any cancer problem — even the most difficult ones, such as pancreatic cancer — exist at Johns Hopkins.

ALTHOUGH EXPERTS have made much progress against pancreatic cancer, there are still far too many people who are diagnosed after the cancer has advanced and spread. Immunotherapy and targeted therapies have been major advances, but there are many who are not helped by these promising treatments.

Elizabeth Jaffee, the Dana and Albert "Cubby" Broccoli Professor of Oncology and one of the world's foremost pancreatic cancer experts, is leading research and patient care in a new direction.


Jaffee

Jaffee created the **Convergence Institute**, where doctors, nurses, astronomers, engineers, computer scientists, physicists, bioethicists, biologists, materials scientists, mathematicians and other experts from a variety of fields will work side by side to amass and apply their knowledge to cancer. Beginning with pancreatic cancer, they will solve complicated and vexing problems, build new technologies, and consider out-of-the-box, creative new approaches that can only be found through this type of directed collaboration. Together, they will plan and chart new cancer prevention, detection and treatment strategies that intricately apply every bit of knowledge available.

It represents a new tactic, different from the assembly line approach that, although useful, applies consecutive contribution of expertise, implementing one thing at a time and offering separate and distinctive components of the whole. Instead, the institute brings a convergence of expertise — in which people come together in synergy to merge their ideas and knowledge into a new whole.

Imagine, for example, Marie Curie, Katherine Johnson, Albert Einstein, Frederick Douglass, Steve Jobs, Leonardo da Vinci, Aristotle, Stephen Hawking and Sally Ride working together, combining their ideas and expertise to solve a problem. This is what Jaffee envisions for cancer.

Jaffee recognized the immense

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talent amassed at Johns Hopkins and had the vision to bring it all together to combat cancer, which is among the most complex diseases. While each new discovery advanced the understanding and treatment of the disease, it tended to also reveal new ways the cancer cell corrupted and disarmed natural biological processes that threaten its ability to survive, grow and spread.

"Cancer is a complicated problem, and to solve this problem, we need more than cancer biologists and cancer doctors," she says.

The answers, she says, lie in the data they are accumulating, but it requires physicists, engineers, computer scientists and others to turn it into meaningful information that can be used against cancer. Real progress will be measured by who is best able to interpret and use these massive amounts of data to help patients.

"Convergence is the only way to assemble the expertise to make use of all the tools available and tailor them to cancer discovery and medicine," Jaffee says. "It will allow us to convert data chaos into data order."

Extraordinary Responders

Sorting out why certain patients with pancreatic cancer exceed all expectations in their cancer's response to treatment is a major focus of the Convergence Institute. Johns Hopkins Kimmel Cancer Center experts call them extraordinary responders.


Laheru

Daniel Laheru, the Ian T. MacMillan Professor in Clinical Pancreatic Cancer Research and co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, says extraordinary responders make up 1% of patients with advanced pancreatic cancer. Among the 500 new patients Laheru and colleagues see each year, just four or five will fall into that category.

This unique group includes patients whose pancreatic cancer spread but now is completely gone. In a disease where only 20-30% of patients survive five years, this type of response to treatment is indeed extraordinary.

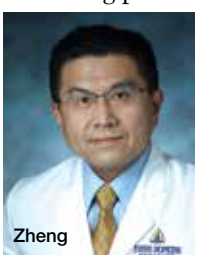
"There is something special about those who defy the numbers, and we want to understand it," says Laheru. Are there similar features about the cancers among extraordinary responders? If there are, and they decipher these complexities, they can use this knowledge to guide treatments — selecting treatments they know will work and steering away from ones that won't — and, their most lofty goal, convert nonresponders to extraordinary responders.

Teams form to develop and study ideas and approaches, and determine which work best and merit further investigation.

One thing extraordinary responders seem to have in common is mutations to BRCA genes, but not everyone with a BRCA mutation responds to treatment. In fact, Laheru says, there are more who don't respond than do, so there is more driving the response than that mutation, and that's what they hope to find.

It is these extraordinary responders who inspired the Convergence Institute to take pancreatic cancer on as its first project.

Blood and tissue samples patients volunteer to provide are already advancing pancreatic cancer care.


Zheng

Experts like **Lei Zheng**, co-director of the Pancreatic Cancer Precision Medicine Center of Excellence, are applying the product of convergence to further advance individualized therapies. As they study the genetic makeup of pancreatic tumors, they are identifying new treatment targets — signals that could be inhibited with drugs to help thwart the cancer. Zheng is developing a system to get these actionable targets on a database that clinicians and researchers can access.

"Once launched, providers could go to a dynamic website to see if their patients have an actionable target in their tumors," says Zheng. "As science develops, the system would update."

Laheru says the Convergence Institute has an all-hands-on-deck philosophy. It is physically located on the seventh floor of the Skip Viragh Outpatient Cancer Building, but in practice, it extends to every specialty — 34 departments among five Johns Hopkins University schools — and includes experts who do not typically have a seat at the table in the world of medicine.

"Engineers, physicists and other scientists we don't typically work with come at a problem from a different perspective. They find clues we don't see," says Laheru. For cancer clinicians and scientists who pioneered the multispecialty approach of bringing together all the medical specialists involved in treating pancreatic cancer to develop a treatment plan, expanding this approach to include experts from other scientific areas makes sense.

They begin with development workshops. A cancer doctor like Laheru explains the problem to the expansive and diverse group of experts who make up the Convergence Institute.

"We speak a different technical language in medicine than an engineer or physicist, so we have to make sure we have a common understanding of the problem," says Jaffee. "Then, working together, we bring our different tools to the problem." Teams form to develop and study ideas and approaches, and determine which work best and merit further investigation.

Jaffee wants to make sure they share information rapidly. She says their colleagues from other fields don't

wait a year for a publication to get the word out on their research, as is often the case in medicine. Instead, they put it out on websites right away so they can share their computation methods and get insights from other experts.

Convergence Institute experts have already begun designing their first studies.

"We're really the only ones doing it clinically," says Laheru. "We're ahead of the curve."

He and Jaffee say support from the Viragh family and the MacMillan Foundation have been vital to launching the institute.

Defying the Odds

For some reason, a small subset of patients with advanced pancreatic cancers have remarkable responses to cancer treatments, seeing their cancers virtually disappear, a response typically unheard of in this cancer type.

They sit in a doctor's office in shock when they learn a persistent ache or pain is actually a consequence of the worst stage of one of the worst types of cancer. They listen in disbelief as they hear the doctor offer little hope for survival.

Then, inexplicably, they become one of the rare patients who have an extraordinary response to treatment, and their cancer fades away. They are unprepared for such a favorable response as they recall the dismal outlook presented upon their diagnosis, and they are reluctant to trust it is real.

Cure is not often a word used to describe pancreatic cancer. Patients are surrounded by information that says they should not be alive, leaving them to wonder how and why. This kind of uncertainty is a breeding ground for worry. When researchers figure out the how and why of extraordinary responders, patients and doctors alike may be able to confidently know a cancer is not coming back.

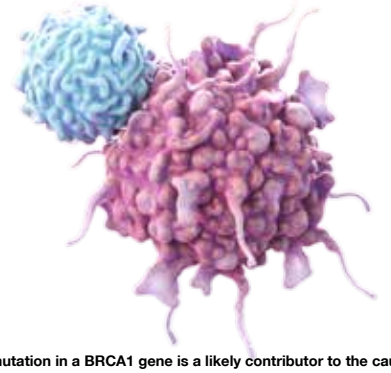
How and Why

Why these patients have such remarkable responses when so many others do not is the question researchers are trying to figure out.

In some cases, these responses are long-lasting. In others, they offer longer survival, with years free of cancer, but then as unexpectedly as the cancer disappeared, it returns and often has spread to other places in the body.

Considered among the world's foremost experts in pancreatic cancer, Jaffee and Laheru are all too familiar with the challenges of obtaining long-term responses in advanced pancreatic cancer.

Treatments, including immunotherapies developed by Jaffee, which have cured some patients, and novel multidrug combinations (see page 21), hold some advanced pancreatic cancers, particularly those with BRCA mutations, at bay.



A mutation in a BRCA1 gene is a likely contributor to the cause of pancreatic cancer, but in a strange twist, it also can make the cancer more responsive to drug treatments. The gene's function is to help make DNA repairs. When it is mutated, it cannot do its job, which helps cancers to form, but it also prevents cells from repairing DNA damage caused by anticancer drugs, so the cancer cells die.

Revealing biological mechanisms, such as BRCA mutations, that may differentiate extraordinary responders from those with cancers that do not respond to treatment is one focus of researchers in the Convergence Institute.

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Advanced cancers of all types remain a challenge. Since cancers originate from our own cells, they have at their disposal all the mechanisms of normal cells, and they exploit them to resist treatment and maintain survival. Extraordinary responders are rare, but the promise — if investigators can use new technologies to identify the unique features in and around the cancer that confer the ability to stave off even advanced cancers — is immense.

The Convergence Institute is at the heart of in-depth research of patients who have extreme responses. It points investigators in new directions, revealing differences in the biology of these cancers and the cells in and around them, to advance therapies for all patients.

Stopping the Spread

Cancer, including pancreatic cancer, kills by invading and spreading to organs, disrupting their vital functions. As it does, it often also evades the best treatments.

"It's difficult to observe what's going on inside the pancreas," says **Andrew Ewald**, co-director of the Kimmel Cancer Center's Cancer Invasion and Metastasis Program. "It is deep inside the body, and imaging such as CT scans and MRI don't have the cellular resolutions to show us what is going on at the molecular level."

The ability to study tissue samples from patients, for the most part, is limited to procedures done in the treatment of the cancer, such as surgery.


Ewald

Ewald says the Convergence Institute allows researchers to work collaboratively to decide what key questions to pursue in research. Together, they can share scarce, precious samples and approach the studies that need to be done in a systematic and efficient way.

"The unique vision it brings is a new way to organize people and space to accelerate and increase their ability to work at the frontier of discovery at an accelerated pace," says Ewald. "So much of success comes from simply getting the right people talking together."

Ewald explains that cancer scientists and clinicians are most likely to collaborate with other cancer experts. They traditionally are located near each other, and are the colleagues they see every day. This obvious and convenient association has merit, but it also limits exposure to other sciences that could inform advances against the cancer.

Programs such as biomedical engineering provide crucial insights and expertise, but many of these experts work within the school of engineering at the Homewood campus. Physical distance makes collaboration less likely. The Convergence Institute brings these and other experts together to broaden the scope of cancer research and bring more brainpower to the most difficult cancer problems.

The 'Google Maps of Cancer'

Technology is ripe to pursue innovative research that could lead to lifesaving breakthroughs in pancreatic cancer. "We've built the tool set," says Ewald.

New computational approaches are providing a never-before-seen view — at the single-cell level — of the tumor and all the cells in and around it that contribute to its survival.

Ewald calls it the "Google Maps of cancer." The fine details in these new technologies offer a detailed view of how and where the tumor exists in the body and how it interacts with surrounding tissues. It's possible to zoom in on spatial features and also pull back to get a fuller view.

"In Google Maps, we can identify a location, look at 6 square miles around it and understand the terrain. What are the unique features of the land, and how much or how little of these features exist?" asks Ewald. "Pathologist **Bob Anders** can do the same thing at the cellular level to provide a map of the pancreas and surrounding tissue and organs."

Provided with any list of proteins, Anders can quantify their abundance, where they are in the tumor, and how they are impacting the growth and spread.

But Anders recalls when they first started gathering this data. The datasets were so large that he and cancer pathology colleague **Janis Taube** couldn't even open the computer files.


Anders

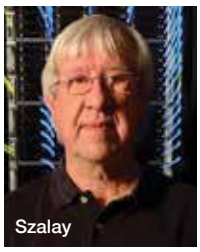
"Our computers couldn't handle the files. They were too big. We needed 1 million lines," he recalls.

"We're physicians, not data scientists, so we didn't know how to fix this problem in the information pipeline," Anders explains.

Of Astronomical Proportion

The problem and potential benefit was literally of astronomical proportion. Anders knew he had critical information that could help patients, but he couldn't access it. That's when Jaffee suggested he talk to Johns Hopkins University astronomer and computational scientist **Alexander Szalay**.

Szalay's night sky project to survey, store, measure and analyze properties of 300 million galaxies required development of a computerized system to analyze the mind-boggling datasets it produced. Anders' datasets of 1 million lines that were crashing his computer were a grain of sand compared with Szalay's datasets of 10 billion lines.


Szalay

Szalay had already dealt with and fixed the problems Anders was facing.

"We're leveraging what Alex learned from the telescope to the microscope to advance our understanding of cancer biology," says Anders. "Alex doesn't know cancer, and I don't know how to analyze the images we get from all the data, but together we can figure it all out. That is the power of the Convergence Institute."

The beauty of the sky server Szalay developed was that anyone could use it. He made the data accessible and usable, which was Ander's goal too. He wanted Jaffee, Laheru, Zheng and other pancreatic cancer experts to be able to sit at a computer and get answers to their questions without needing an IT expert there to translate.

The images of the night sky that Szalay's datasets created are remarkably similar to the terrain of the cancer cell and its environment, providing a high-quality imaging system for microscopic sections of tumor biopsies. Jaffee and other pancreatic experts can use it to determine how likely a cancer is to respond to different types of immunotherapy or other treatments. Deep-learning algorithms, derived from artificial intelligence, provide sophisticated models that will predict what treatment is the best option for a patient.

"What leads to certain patients having remarkable responses? This technology allows us to find the answer."

"It's all about prediction," explains Anders. Biomarkers — clues within the DNA of the cancer and surrounding cells that point to how the cancer will behave and respond to treatment — predict survival. Anders calls it predictive precision cancer medicine, using the technology to differentiate, tells them, he says, "these patients will benefit from this treatment, but these patients won't."

With the Google Maps of cancer Anders created with the help of Szalay, researchers can see the proximity of the tumor cell to immune cells, calculate an average proximity, learn what specific types of immune cells are excluded from the environment, and more.

One of the first uses was measuring the distance between cells that contained certain proteins — PD-1 and PD-L1 — that are among several checkpoints, or on/off switches, of the immune system.

Under the pathologist's microscope, PD-L1 is seen as forming an armor around cancer cells that protects them from the immune system. Immunotherapies called checkpoint blockers disrupt cancer cells' ability to hijack PD-L1 signaling to avoid detection and destruction by immune cells. PD-1, an immune checkpoint,

often works in conjunction with PD-L1 to help cancer cells evade detection by the immune system. Seeing this helps determine which patients might benefit from PD-1 and/or PD-L1-blocking drugs.

Now, Anders, says, they are gathering the same information on other immune checkpoints and beginning to look for these kinds of biomarkers in precancers to see when in the cancer process the immune system becomes disabled.

"We could never answer these questions without the Convergence Institute and these new kinds of technology," says Anders.

Using Science to Chase Individual Successes

Anders is most excited about the difference technology is making in immunotherapy.

"We have never seen anything of this magnitude in cancer," he says.

He was part of the Kimmel Cancer Center research team that made the seminal finding in 2017 linking a DNA spellchecklike error, known as mismatch repair deficiency, to response to immunotherapy, leading to FDA approval of the drug pembrolizumab for patients whose cancers contain this genetic repair defect. It was the first time a drug was approved based on a specific genetic profile without regard to where in the body the cancer started.

The finding emanated from a clinical study of a PD-1 checkpoint-blocking drug done at the Kimmel Cancer Center. The trial was open to all patients with advanced cancers and included many colon cancer patients. Among 20 colon cancer patients treated, only one patient responded, but getting to the bottom of it and identifying mismatch repair deficiency as the driver of the response changed the cancer paradigm from a cancer-specific model and opened the floodgates to the exploration of immunotherapy across all cancer types.

"We've always wanted to use science to chase individual successes. What leads to certain patients having remarkable responses? This technology allows us to find the answer," says Anders.

The first checkpoint blocker was studied in 2011, and now there are more than 50 approved immunotherapies. Anders wants to see this success occur in pancreatic cancer, which to date has seen only limited response to immunotherapies.

He is collaborating with other experts to use technology to solve the mystery of why pancreatic cancer suppresses the immune system. T cells are there, he says, and researchers think they are the right T cells, but there are other inhibiting factors they don't yet know about that are stopping the T cells from performing their job as cancer fighters. He hopes this research will show them why some patients respond magnificently to pancreatic cancer vaccines — the extraordinary responders — and others have limited or no response. What is unique about the extraordinary responders?

The opportunities to help patients are limitless, like catching lightning in a bottle.

"We think pancreatic cancer stacks them up," says Anders. Immune checkpoints are one barrier, but he believes there are many others they will find through research in the Convergence Institute that work together to give pancreatic cancer its survival benefits.

"That's why we want to measure so many markers," says Anders. "We've misunderstood many cancer mechanisms, and we think the clues to what makes pancreatic cancer such a lethal cancer are there for the finding."

The Immune System Is Different

These will be practice-changing discoveries, he believes. The immune system may be a better predictive marker of how a cancer will respond to treatment than the size and spread of a tumor. It is perhaps the only cancer therapy that can beat back even the worst cancers — those that have spread.

He compares the complexity of the cancer cell with the whack-a-mole carnival game, in which the player knocks one mole back into a hole, only to have another pop up. For many cancer therapies, Anders says, we use a drug to put pressure on one cancer driver, and the tumor mutates and escapes.

"The immune system is different," he says. "When the immune system works, it stays working." This durability is one of its most unique features, but it makes sense. The job of the immune system is to patrol for foreign invaders. If it recognizes the cancer, it should stay locked on its target until the cancer is gone.

It's not easy research, but if the Convergence Institute assembles the experts who can decipher it, he believes the opportunities to help patients are limitless, like catching lightning in a bottle.

In addition to 50 approved immunotherapy drugs — more than all other cancer drugs approved in the last decade — these treatments are now becoming first-line therapies. Even better, they are tweaking the immune system before therapy ever begins. Called neoadjuvant therapy, giving immunotherapy before surgery has greatly reduced the size of tumors and, in some cases, even eliminated the cancer in certain patients.

When tumors are removed in surgery, they are studied using Szalay's technology to measure changes in beneficial T cells — things that are suppressing the immune reaction to cancer and other influences on the immune cells and cancer cells.

"Before, we could only measure one thing at a time, and in cancer, there is never just one thing happening," says Anders. "Now, we can measure multiple

The Convergence Institute unites the immense talent across Johns Hopkins to advance research for all cancers, with a focus on ensuring that these discoveries reach patients throughout region.

Meaningful data will be interpreted and used against cancer to help patients.

They will solve complicated and vexing problems, beginning with pancreatic cancer.

Collaboration will advance new technologies and out-of-the-box approaches.

New cancer prevention, detection and treatment strategies will be implemented.

Experts from many fields work side by side to apply their knowledge to cancer.

things and compare and evaluate them on the fly to quickly tell if a treatment is working."

The more data we gather, the more cancer discoveries will be made, Anders says. "I want even more data points, more ways to look at differences among cells," he says. Businesses use data to predict when a person is going to buy a product, the specifics of the product they will buy, how often they will buy it and more. Computer engineers working in the Convergence Institute want the same extensive data for cancer medicine.

Anders wonders, "If we can use data to predict when someone is going to buy a car, can we figure out a way to use data to predict who is going to develop or die of cancer?"

With Szalay's technology, Anders says they can go after these kinds of questions. In this area, he says, Johns Hopkins is ahead of the game. Although others have created databases, they do not have the same interactivity and responsiveness as the one Szalay created.

In cancer, time is always important, and converging on it with such breadth and depth means progress should be accelerated.

"This should help us avoid sitting here 10 years from now saying, 'How did we miss that?'" Anders says, "We've made observations through the convergence of expertise that will change the lives of patients forever. There are going to be several hundred thousand people alive because of what we do. The only way to top this is to extend this success to even more patients."

Ultimately, it was the promise of this kind of success that changed Anders from a pessimist to an optimist. As a medical student, he saw so much laboratory research that did not translate into improvements in patient treatment. He had made up his mind that he would never pursue a career in oncology. The untapped potential of cancer immunology and progress being made at the Kimmel Cancer Center through collaboration led him to see things differently.

Anders thinks about the first patient with melanoma treated in the Kimmel Cancer Center's PD-1 immune checkpoint blocker immunotherapy trial. "She had melanoma everywhere. Immunotherapy worked for her. It saved her life. That changed everything for me."

IN CANCER, TIME IS ALWAYS IMPORTANT, AND CONVERGING ON IT WITH SUCH BREADTH AND DEPTH MEANS PROGRESS SHOULD BE ACCELERATED.

Informed by Math

Every problem — even cancer — can be informed by math, says **Elana Fertig**, co-director of the Convergence Institute and director of Quantitative Sciences.

Fertig, who began her career as a weather forecaster, made a career change to cancer researcher because of cancer's complexity. In predicting weather, Fertig says the challenges were taking different sources of data and integrating them with computer models to improve forecasts.

Now, she is applying the same strategy to cancer: gathering data and developing computer models to analyze it to predict how a cancer will behave and will respond to different types of treatments.

"In cancer biology, we don't know what we don't know," she says. "The ability to think about extracting new information from new technologies in a new way, and using math to uncover biological principles from that data is very exciting."


Fertig

In the Convergence Institute, she has an opportunity to conduct research in which math is the driving principle to discover new biology. This unique perspective, mixing it up and adding different disciplines, is putting forth new ways to predict how cancer cells or cells in the environment that comprise a tumor behave and interact to support a cancer to progress.

Researchers tend to sort cells into different categories based on their appearance under a microscope or, for differences that are more visually subtle, the behavior of a handful of genes. But Fertig says math is the key to revealing even more distinctive differences and similarities.

Her research teases apart reactions and interactions between immune cells and tumor cells as cancers develop resistance to treatment. Almost all cancers — even pancreatic cancers — initially respond to treatment. It is cancer's ability to morph into something new to resist and escape what we throw at it that kills.

Fertig developed AI methods that decipher complex circuitry and interconnectivity of gene activity controlling cell growth, death and other behaviors in tissue and organ development and relates this gene activity to what occurs in other tissues and across different species.

She developed a system called scCoGAPS that searches for patterns that characterize cells based on their expression levels. A second method, called projectR, first studied in the mouse retina, used the patterns scCoGAPS revealed to relate the cells in the developing retina to cells in other systems, including the adult mouse retina, the developing human retina, the developing brain and other cell types throughout the mouse body.

"From a basic biology standpoint, this challenges the notion that a given

cell type is really defined by a limited set of genes," she says. "We show that these patterns of genes can be interrelated, and that broader patterns across genes are preserved from sample to sample and context to context."

She is using her findings to gauge patients' response to cancer therapies by the activity of a single gene or a handful of genes. Using scCoGAPS and projectR may show a more complete picture of gene activity that could help researchers develop better ways to target cancers.

How we rewire the microenvironment to sensitize patients to immunotherapy is among the ideas Fertig and collaborators are pursuing.

The research models we have, such as biological tumor models, are good and have led to tremendous progress, but there are also recalcitrant problems remaining that need a different approach.

The goal of the biological tumor models is to kill cancer cells, but when the cells die, Fertig points out, they are no longer accessible to study. She uses math to offer new models.

Combination therapies are a prime example. "There is not enough time or patients to conduct a clinical trial on every potential combination," she says. "In many ways, it is about organizing the data in the right way, but figuring out the right combination — what provides the best outcomes for most cancers — can be solved with math."

The Convergence Institute is helping her make this math-to-medicine connection.

"We are bridging experimental models and divides by building a community of people who are cross-disciplinary to engage with the Cancer Center," says Fertig. "We're getting at things we haven't gotten at before and looking at them in a new way, taking principles from other fields to figure out how to overcome failures in treatment."

Most laboratories start with a pipette to do an experiment. Fertig and her collaborators start with data. "We go in the reverse direction," she explains. "We start with the data that has already been generated, and then we go to the lab to see what we can learn about it."

In one case, Fertig and her collaborators found applying her AI methods to a public dataset related to the immune system led them to a new type of cell that influences treatment resistance. Now, they are using the discovery to guide therapy by identifying the best type of immunotherapy for each patient and how it should be given.

The goal of convergence, she says, is to translate these discoveries to the clinic, "and Johns Hopkins is set up to do it right. This is real team science, and it's exciting to look at things in a new way. Cancer is a puzzle, and we piece it together using different technologies and different areas of expertise that will get us to the answers."

The Single Cell

Fertig is collaborating with researcher **Luciane Kagohara** on a specialized technology called single cell sequencing that offers a detailed view of the tumor composition and enables scientists to measure all cell types in the tumor and examine their function. With the rapid advances in the field, it's now possible to zoom in on spatial features and identify how those cells interact with one another without dismantling the tumor samples. This approach can help scientists and clinicians discriminate between treatment resistance built into the tumor and resistance that is acquired during treatment.

"Essentially, it gives researchers the ability to reveal and understand the instruction manual for every single cell in the tumor, immune and stromal cells, and how their distribution in space is driving cancer development and response to immunotherapies," says Kagohara. The researchers hope to learn why immunotherapy often works well in one patient and not in another. "If we can understand these mechanisms, we can choose therapies better," she says.

Elana Fertig, Ph.D., Luciane T. Kagohara, Ph.D., and Elizabeth Jaffee, M.D., received a three-year, $1.47 million award from the National Cancer Institute Informatics for Technology for Cancer Research for "Single-cell and imaging data integration software to spatially resolve the tumor microenvironment."

Imagine a smoothie that contains a mix of ingredients: strawberries, blueberries, raspberries, milk, sugar and more. Once everything is blended together, it's difficult to distinguish one component from another and what it adds to the mix. In some ways, single cell technology is analogous to getting a look at each ingredient in the bowl before it goes into the blender.

There are differences from one tumor type to another, but even among

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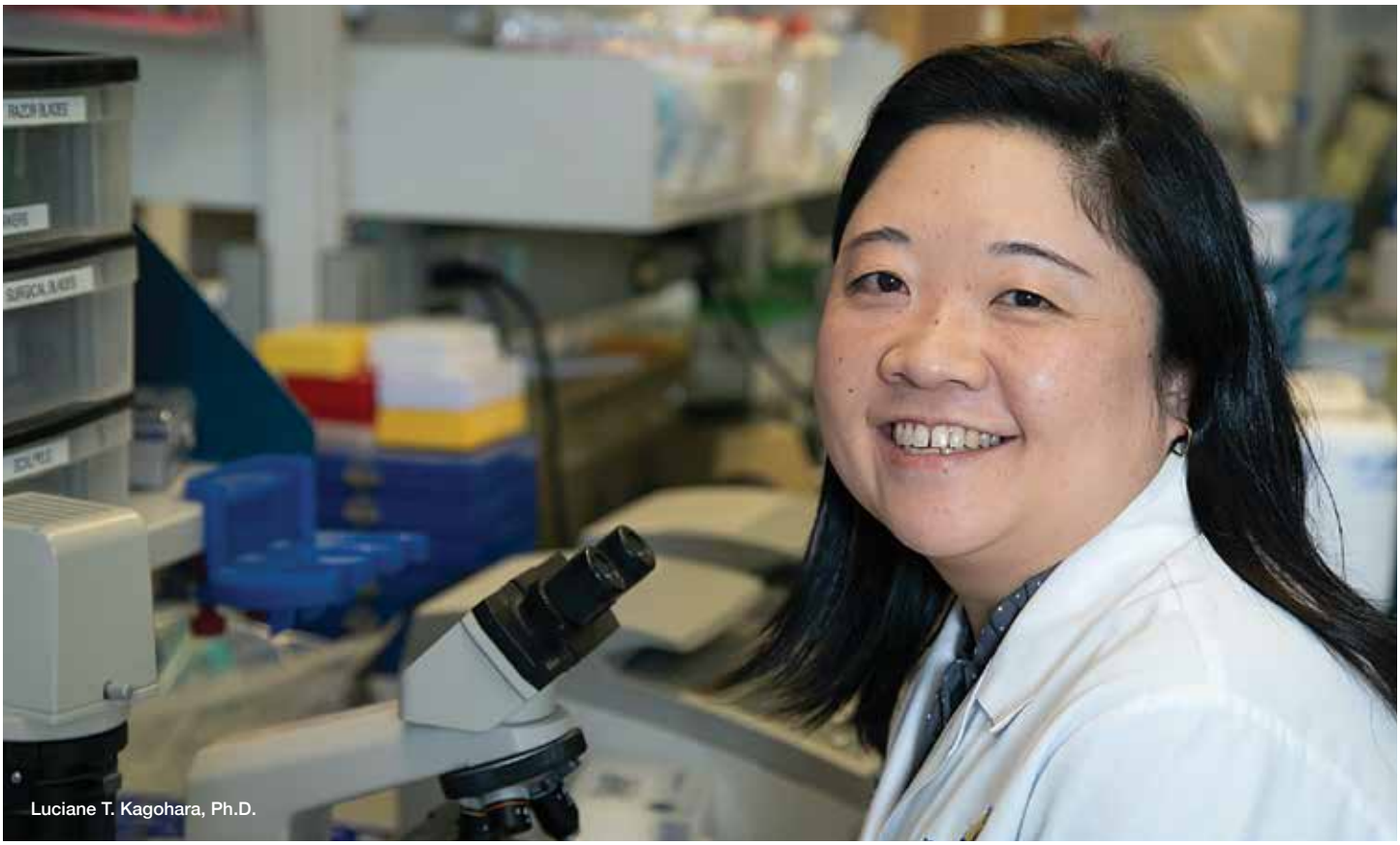


Luciane T. Kagohara, Ph.D.

Daniel Laheru, M.D.

seemingly identical tumors with the same mutations, there are hidden variations in the mix. Often, experts point out, it is these differences that hold the key to why certain cancers respond to treatment and others are resistant.

Kagohara and collaborators want to know and understand the signals influencing and being generated by each cell. Her research will reveal, for any given pancreatic tumor, what fraction of cells comprise the whole — what percentage is tumor cells, stromal cells, immune cells and other cell types. With this information, she can go back and look at each of these cells individually at the molecular level. What are the signaling pathways used by the cancer most frequently or, conversely, infrequently? In essence, she is a creating a blueprint for what goes on inside pancreatic cancer.

The ultimate goal is making cancer therapies work better. She is collaborating with Zheng to try to turn cold pancreatic tumors — those that do not attract an immune response — into hot tumors, or a tumor that activates the immune system. If she can identify cells that are keeping immune cells away from tumors, perhaps that signal could be blocked to make immunotherapies work.

Organoids

Small, natural replicas of human tissue, called organoids, are another example of a new technology accelerating cancer research.

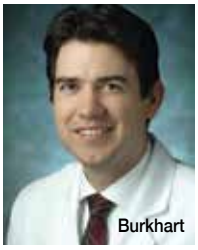
"The biggest problem we have in managing pancreatic cancer is that we don't know before we start therapy which treatment might work the best for each patient," says pancreatic cancer surgeon **Richard Burkhart**.

He and pathologist **Laura Wood** are using pancreas organoids — ultratiny replicas of a patient's pancreas, grown from their own cells — to better understand the mechanisms of how a cancer originates and grows, and as a unique way to test responses to treatments.

One area of cancer research looks to the genetic mutations within the DNA of a cancer cell to identify drugs that could target those alterations and change the trajectory of the cancer, but Wood and Burkhart say that only paints a partial picture of the cancer.

"The genome doesn't tell us everything we need to know," Burkhart says. That appears to be particularly true in pancreatic cancer, which has only four main genetic drivers. As a result, experts cannot always tell from genetics which treatment is likely to work best for patients.

Real-life experience drove him to look for a better way to model cancer growth and behavior. As a surgical resident in 2014, he did protein biomarker research.


Burkhart


Wood

"We had a biomarker we thought would tell us whether a patient would respond to chemotherapy," he recalls. After three years of research, the biomarker failed in late-phase study. That disappointment pointed him toward organoid research.

"I was drawn back to the concept of a black box, in which basic theory dictates that you may not need to know everything about a system or cell as long as it can be modeled accurately enough to get the information we need," he says.

It spurred his collaboration with Wood to create pancreas organoids. These natural replicas mirror the cancer in the patient's organ where it starts and grows. They reflect the genetic mutations present in the cancer as well as other contributors, such as chemical changes or differences in RNA that influence how cells behave.

The organoids are created from patient tissue obtained during biopsy or surgery from the lining of pancreas ducts where cancers begin. As the organoids grow in the laboratory to about the size of the tip of a pen, the structures that host the cancer develop, forming a more accurate representation of a patient's tumor in a natural biological environment that supports the cancer's growth.

Burkhart does about 150 pancreatic cancer surgeries a year. He has a vendetta against the disease and resents its ability to destroy lives. He channels that emotion and energy into his organoid work, going from the operating room to the laboratory, tumor sample in hand, to grow an organoid and look for ways to get the upper hand on the cancer.

Wood and Burkhart think the organoids reflect the tendencies of the actual patient tumor. For example, if an organoid grows more quickly, it could be a warning sign that the tumor may be more aggressive and dangerous.

It takes one to two months to grow the organoid, about the same time it takes patients to recover from surgery. Burkhart and Wood say they can introduce anticancer drugs into the organoid to see how the cancer reacts. By the time the patient has recuperated from surgery, they would have a drug treatment plan ready.

Right now, their research is aimed at proving that drugs that work against a cancer in an organoid have the same effect in patients. Once they confirm this, patient-derived organoids could be used to guide treatment.

"This is a platform for directly testing standard of care and newly developed drugs, including immunotherapies, in cancers," says Burkhart.

Benign or Cancer

Wood is also using organoids to examine small growths that occur in the ducts of the pancreas, called intraductal papillary mucinous neoplasms, or IPMNs. In some people, these growths become pancreatic cancer, so Wood is taking a closer look, comparing IPMNs that look like they are making the transition to cancer with those that look benign. She is collaborating with pathology colleague **Liz Thompson** and Jaffee to see how they are different genetically, how the immune system sees them and how they change over time.

"We are trying to figure out what shuts down to allow them to transform to cancer," says Wood. She says they've

"It gives me goose bumps knowing that the work we're doing in the Convergence Institute and all that we've learned will save lives."

— **Elizabeth Jaffee, M.D.,**
pancreatic cancer expert and Director of the Convergence Institute

observed T cell responses early on that diminish as the IPMNs move closer to becoming cancer. Wood turned to organoids to understand the mechanisms that are driving that change.

IPMNs are fairly common, and being able to differentiate dangerous ones — threatening to become cancers — from the harmless, benign type can guide therapy and pancreatic cancer prevention strategies.

"We don't want to do surgery on all of them," says Wood, adding that there is considerable controversy about how to treat them. She wonders if immunotherapy may be a way to safely control the lesions that appear to have lost the attention of T cells and are beginning to transform into pancreatic cancers.

Her research represents a new frontier. Wood and collaborators are among the first to use a human organoid model to study the immune system's role in IPMNs' progression to cancer.

"Most cancers start from precancerous lesions. The cancer overgrows and converts to a malignant tumor," she explains. "Most human models look at a single point in time, but using organoid models of cancers and precancers, we can observe what changes as precancers convert to cancers."

They may be able to identify genetic drivers of the conversion and potential ways to intervene.

Wood is also collaborating with engineering colleagues to create a 3D model of IPMNs. Their work makes lesions transparent, so all they see is the inner workings — how cells invade arteries to develop a blood supply for nourishment to grow, whether the shapes of cells correlate with other favorable or unfavorable clinical features, what immune markers are present, what gene mutations are there and if they are related to the growth of the cancer, and also what epigenetic — or chemical alterations to genes — could be cancer drivers.

Wood says mutations in a gene called KRAS are common among IPMNs, but there is something else that occurs before the KRAS mutations to start the process. Understanding what that earlier insult is will help identify people most at risk for developing pancreatic cancer.

"THE BREADTH OF EXPERTISE AT JOHNS HOPKINS IS OUR GREATEST ADVANTAGE. WE CAN APPLY MULTIPLE TECHNIQUES TO THE SAME PROBLEM AND COME UP WITH APPROACHES WE WOULD NEVER HAVE COME UP WITH INDEPENDENTLY."

One candidate they've identified is a gene called SMAD4, believed to promote cancer invasion. She will be studying the gene in her organoid models.

Wood also plans to study immunotherapies in the organoid models to develop precision medicine approaches to treating patients. She will create organoids from patient tumors and treat them with individualized cancer vaccines aimed at the specific drivers of each patient's cancer, to see how the organoid cancer responds to the treatment. If the vaccine works against the cancer grown in the organoid model, it would be worth trying in the patient.

"We can grow the patient's actual tumor and see how it responds to interventions," says Wood. "We can also grow many replicas of the tumor to capture differences in responses among a variety of drug treatments."

Researchers can also tell what the drugs are doing to the gene expression in tumor cells or the cells surrounding the tumor.

In an individualized medicine approach, Burkhart is growing organoids for every patient with metastatic pancreatic cancer to test drugs and drug combinations to see what works best.

"How dangerous is my tumor? Has it spread? How do I extend my life? Will therapy work? That's what patients care about, and that's what all of the expertise gathered in the Convergence Institute is set to find answers to," says Ewald, who is collaborating with Wood and Burkhart.

Wood agrees. "Any time you get a wide variety of perspectives, you get new ideas," she says. "The breadth of expertise at Johns Hopkins is our greatest advantage. We can apply multiple techniques to the same problem and come up with approaches we would never have come up with independently."

This kind of work, they say, has never been done before.

A New Era

For the 56,000 people diagnosed each year with pancreatic cancer, the Convergence Institute provides hope and optimism that this new kind of research collaboration will reveal the knowledge that explains the why and how of extraordinary responders. As they understand their remarkable responses, they can assure these patients of a lasting response and also use that knowledge to extend this promise to more patients, making the extraordinary ordinary.

It also fulfills the aspirations of Jaffee and the clinicians and researchers collaborating with her who, through convergence, now have the tools to fully understand pancreatic and other cancers.

"We're in a new era. I've been researching pancreatic cancer for 25 years, and I am very optimistic that we are on the verge of turning this very deadly disease into at least a chronic disease patients can live with, says Jaffee. "It gives me goose bumps knowing that the work we're doing in the Convergence Institute and all that we've learned will save lives."

RISK MANAGEMENT

Earlier Recognition and Intervention

Elliot Fishman, M.D.

Pancreatic cancer is rare. "If you stand in a room of 100 people, 99% of the time, none of them will get pancreatic cancer in their lifetime," says **Alison Klein**, director of the National Familial Pancreas Tumor Registry at Johns Hopkins. That's the good news. Despite its rarity, however, pancreatic cancer is one the of the leading cancer killers. An astounding 80% of pancreatic cancers are diagnosed after they have already spread, leading to the disease's high death rates.

Klein

Klein sees plenty of room for improvement. Like many cancers, pancreatic cancer can be cured when detected early. She is focused on identifying ways to recognize and help the people most likely to develop pancreatic cancer. She is revealing the path to pancreatic cancer, following genetic clues, tracking family history, scrutinizing lifestyle factors, and studying pancreatic cysts and other changes in the pancreas to chart the disease from its origin and pinpoint opportunities to stop the cancer.

"The first thing we need to do is intervene in the highest-risk populations," she says.

Pancreatic cancer is widely recognized for its high death rates, but some studies, Klein says, show that it's even worse for African Americans, indicating they are 20% more likely to develop it. There are very few studies aimed at understanding the reasons, she says.

"We know that disparities in diagnosis and care are more prevalent among African Americans, and at least in some studies, African Americans who received quality care did better," she says. Klein believes we also need to study the genetic code of African American patients with pancreatic cancer to address disparities. Although she has been working to study the genetics of pancreatic cancer for over 10 years, these earlier studies did not include African Americans. They are needed, she says, to identify increased risk factors caused by access to care compared with those from genetic causes and also to ensure African Americans benefit from the targeted treatment and prevention studies guided by genetics.

In collaboration with investigators at other cancer centers, Klein is leading a study of 2,000 African Americans to look for genetic differences among 1,000 pancreatic cancer patients and 1,000 healthy participants.

"We know genetics play an important role, and there may be some that are specific to populations. Can we drill down to a specific risk profile for African Americans?" Klein asks. For many diseases, the risk profiles developed in European populations often don't work as well in African Americans. She will begin with whole genome sequencing — a complete look at the DNA, the instruction manual for cells — of the 2,000 study participants. Klein points to the discovery that ataxia telangiectasia mutated, or ATM, gene mutations increase the risk of developing certain types of cancer, including pancreatic cancer, among people of European heritage. These mutations occur in about 3% of pancreatic cancers in European Americans. "We don't know if this is true among African Americans," she says. "These things don't always translate, but we need to find out if these findings are relevant to African Americans."

Other risk factors, she says, could be lifestyle related. Obesity is a risk factor for pancreatic cancer and for type 2 diabetes. African Americans have a higher rate of type 2 diabetes,

which is also linked to a higher risk of developing pancreatic cancer. In a chicken-or-egg scenario, Klein is working to figure out when diabetes causes pancreatic cancer and when pancreatic cancer causes diabetes. She knows that at least a small subset of patients with diabetes are destined to develop pancreatic cancer. "It presents and looks like regular diabetes, but within three to six months of their diagnosis with diabetes, we find pancreatic cancer," says Klein. "If we could identify this type of diabetes and do advance screening, we could potentially change the outcomes."

In collaboration with **Michael Goggins,** pancreatic cancer gastroenterologist and a co-leader of the SU2C- Lustgarten Foundation Pancreatic Cancer Interception Dream Team, Klein is also taking a closer look at genetic risks. About 5-7% of pancreatic cancer patients have a gene mutation in one of 12 known genes, including BRCA1 and 2, ATM, and CDKN2A. These genetic clues may aid in early detection and treatment for those at highest risk, Klein says. "If we could identify family members of patients who have one of these mutations, we could get them into screening," she says. In their study, in collaboration with the Dana-Farber Cancer Institute, they are testing 1,000 pancreatic cancer patients for these gene mutations or individuals with a family history of pancreatic cancer. Cancer-free relatives who are also found to have the same mutation are given an opportunity to participate in a screening study aimed at detecting pancreatic cancers at the earliest stage, before they can be seen in imaging.

"Uptake of genetic testing in relatives of pancreatic cancer patients is low," Klein laments. "We need to figure out ways to increase participation." Making genetic testing more accessible, perhaps through at-home testing kits and connections to genetic counselors and screening programs, may be one approach. Potentially, just providing family members with information about the genetic connection to risk of pancreatic cancer may increase genetic testing.

In addition to screening, Klein notes that identifying mutations can also guide treatment. One example, she says, are PARP inhibitors — drugs that augment the benefit of other treatments by preventing cancer cells from repairing DNA damaged by chemotherapy or radiation therapy. They are now an FDA-approved treatment for pancreatic cancer patients with BRCA2 mutations.

"IN THE LAST 10 YEARS, WE'VE BEGUN TO IMPROVE SURVIVAL BY DETECTING THE CANCER EARLIER AND MAKING TREATMENT BETTER."

Klein developed a computerized tool to make sense of genetics and pancreatic cancer risk."Even if there is a 100% chance that an individual carries a pancreatic cancer gene, the risk of developing the disease is only 10-25% over the person's lifetime," she says. "Although it's rare, the need for screening in these people is important." Called PancPRO, Klein's tool computes an individual's lifetime risk of developing pancreatic cancer. "We know how genes behave, and coupled with information about a family — who has the disease, their age, family size and causes of death — our model can provide a good estimate of an individual's risk," she says. Klein is currently working to expand PancPRO to take into account more risk factors, including diabetes and smoking.

Imaging may also reveal new clues. Radiologist **Elliot Fishman** is


Fishman

exploring how it could get more pancreatic cancers diagnosed at an operable stage. He is leading a Lustgarten Foundation-supported research team that is developing an algorithm to detect early-stage pancreatic tumors and abnormalities. Right now, the algorithm — nicknamed Felix — is learning to identify healthy and diseased pancreas tissue on patient scans and to distinguish cancer from other abnormalities. "There are millions of CT scans done each year that include a view of the pancreas. Using these scans, the algorithm can be trained to pick up subtle changes that might indicate early pancreatic cancer. Felix has a better than 90 percent accuracy picking up tumors on CT scans," says Fishman.

Pancreatic cysts are another example of changes that can sometimes be a precursor to pancreatic cancer. Pancreatic cysts are found in 4% of people in their 60s and 8% of people over 70, according to other published research. That means some 800,000 people with pancreatic cysts are identified each year in the U.S. alone, but only a small fraction will progress to cancer. The key is distinguishing harmless cysts from those that will lead to cancer.

A new test, called CompCyst (for comprehensive cyst analysis) developed by Kimmel Cancer Center researchers, is becoming available to guide clinical decisions in patients with pancreatic cysts. This includes identifying patients who should have surgery to remove their cysts, patients who may benefit from monitoring only and patients who will require no care for their cysts. The test was created with patient data, including clinical impressions and symptoms, images from CT scans, and molecular features, such as DNA alterations within cyst fluid.

"Detecting pancreatic cancer is a challenging problem," Klein says. "We've learned so much, and we're beginning to see the bar shift. In the last 10 years, we've begun to improve survival by detecting the cancer earlier and making treatment better. As we make progress in screening high-risk populations, we will be able to extend what we learn to screen for the cancer among the general population."

The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care attracts the most accomplished young investigators interested in pursuing a career in pancreatic cancer research and treatment. By training with established investigators, Skip Viragh Center fellows are helping advance the science and bringing much-needed new therapies to patients.

YOUNG INVESTIGATORS

Trailblazers in the Fight Against Pancreatic Cancer

Improving Immune Therapies

Won Jin *(pictured)*, assistant professor of oncology, is exploring a new target

called PTPN22 with the aim of improving immune therapies for pancreatic cancer. PTPN22 is a protein that regulates the function of immune T cells, Jin says. People born with mutations in the gene are at higher risk of autoimmune diseases — conditions in which a person's own immune cells attack healthy organs and cells. Following this clue, Jin took a closer look at the potential role the gene could be playing in cancer immunity and found that it puts the brakes on T cells, stopping these foot soldiers of the immune system from going after cancer cells. In mouse models, Jin found that when PTPN22 is blocked, an immune response to the cancer starts. Jin is working with colleagues at Purdue University on a new drug that blocks PTPN22, which he hopes to ultimately study in clinical trials.

He is also focused on new technologies that can accelerate cancer biomarker discoveries. For example, using a technology known as mass cytometry, which provides data on more than 40 characteristics of cells, Jin is helping **Dung Le**, **Katie Bever** and **Elizabeth Jaffee** evaluate immunotherapies for pancreatic cancer. He is performing immune profiles of tissue and blood obtained from patients before and during treatment with a variety of immunotherapies to monitor how the immune system responds. His goal is to identify biomarkers that can tell if an immunotherapy is working and predict patients most likely to benefit.

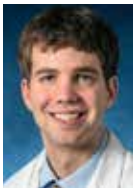
Killer Instinct

Working in the laboratory of Cancer Invasion and Metastasis Program co-director **Andrew Ewald**, **Isaac Chan**

(pictured) wants to better understand the interaction among immune cells and metastatic cancer cells. He developed unique and complex tools to study how breast cancer cells escape the watchful patrol of the immune system and spread to other parts of the body. Although Chan is working in a breast cancer model, he says his findings could be applied to pancreatic cancer and other cancer types. His research focuses on a type of immune cell called the natural killer cell, or NK cell. These cells work to stop cancer cells from spreading, but cancer often figures out a way to shut them down. Chan wants to see if he can reverse the process. If he can use his laboratory model to figure out what cancer cells do to shut down NK cells, he hopes to identify drugs that will reactivate the natural killer cells.

Making Treatments Work Better

When cancer cells are damaged by chemotherapy or radiation treatment, repair mechanisms are engaged to fix



the damage and save the cell. **Eric Christenson**'s *(pictured)* goal is to kill cancer cells by shutting down their ability to make these repairs. Blocking them, he says, may have two benefits: causing cancer cells to die outright and improving response to immunotherapies. Damage to cancer cells is characterized by mutations to the cell's DNA. Enough of these mutations make cancer cells more noticeable to the immune system. "Small numbers of mutations are bad for us and good for the cancer. A lot of mutations are bad for the cancer and good for us," Christenson explains. His goal is to keep the cancer from walking that fine line between too few and the right number of mutations by using a drug that works through a mutation-promoting pathway called APOBEC to turn repair mechanisms on and off. Laboratory studies in human cells were promising. Studies are ongoing, and Christenson says the ultimate goal is to make existing treatments work better.

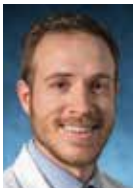
New Ways to Intercept Cancer

Jackie Zimmerman *(pictured)* is among an increasing number of cancer

researchers taking a closer look at microRNAs and how blocking them with drugs could stop or slow cancer formation, extend survival, or even be biomarkers that mark new cancers early before they can be detected through imaging. She explains that although microRNAs do not impact cancer through direct mutations, they function to regulate gene expression, which results in tumor-suppressive or, conversely, tumor-growth-supportive activities. Using organoids — tiny 3D representations of human organs derived from tumor tissue removed in surgical biopsies and treatments — Zimmerman is studying the potential of drugs that block microRNAs to intercept cancers and stop them in their tracks.

Immunotherapy Studied in Aggressive Pancreatic Cancer Subtype

Clinical trials of immunotherapy are planned for a rare and aggressive type of pancreatic cancer known as adenosquamous cell. Because it accounts for less than 5% of pancreatic cancers, it is poorly understood and has no clinical studies. Standard therapies are currently the only options for patients, who often have poor responses. Taking a closer look at the little-studied cancer, pathologist **Liz Thompson** found higher immune checkpoint expression and more cancer-killing T cells in the cancer than are typically found in pancreatic cancer. Immune checkpoints provide stop-and-go signals to the immune system. Cancer cells use them to shut down immune responses to cancer.



Based on these findings, **Christopher Jakubowski** *(pictured)* is working with pancreatic cancer experts **Nilo Azad**, **Daniel Laheru** and **Elizabeth Jaffee** to develop a clinical trial of anti-PD-1 immunotherapy — a drug treatment that removes restraints cancer cells place on immune cells — for patients with advanced adenosquamous pancreatic cancer. Since the cancer is so rare, Jakubowski is collaborating with the Mayo Clinic to reach enough patients to conduct a clinical study. Biopsies will be taken before and after treatment to advance laboratory research and gain a better understanding of the cancer. Part of what they hope to learn is what causes the cancer to have its squamous cell component — one of the characteristics that make it less responsive to standard treatments — and what leads to the more favorable immune environment. What they learn, Jakubowski says, could help adenosquamous cell patients and provide new insights that may also help make immunotherapy work better in this cancer and more common types of pancreatic cancer.

A New Kind of Cancer Vaccine

A pancreatic vaccine that targets the KRAS gene mutations most common in pancreatic cancer will be studied in patients who have had surgery and chemotherapy as a way to prevent the cancer from coming back. **Neeha Zaidi** *(pictured)*, assistant professor of

oncology, is collaborating with **Elizabeth Jaffee**, co-director of the Skip Viragh Center, on the vaccine study supported by the Stand Up to Cancer Interception Dream Team and says the goal is to guide the immune system to attack cells that contain these mutations. The vaccine should have broad application as one of the genes targeted, the KRAS gene, is mutated in 95% of pancreatic cancers, and earlier research demonstrated an immune response to KRAS. This "off-the-shelf" approach increases its reach and may be a more economical alternative to personalized vaccines made for individual patients to target the specific mutations unique to each patient's cancer. Instead, this vaccine uses peptides, or protein fragments, from the commonly mutated KRAS gene across the majority of pancreatic cancers. These protein fragments send signals that may set the immune system into action. The vaccine is also combined with immune checkpoint-blocking drugs — immunotherapies that remove restraints cancer cells place on immune cells — to improve effectiveness of the vaccine. "The vaccine in combination with immune checkpoint inhibitors should be able to instruct the immune system to take out any cell that contains these mutations," explains Zaidi, who says they will be testing the vaccine in other cancers that contain KRAS mutations, including colon and lung cancers. This vaccine will also be used in a follow-up clinical trial aimed at preventing pancreatic cancer in patients who are at high risk of the condition.

Approaching Treatment from the Patient Perspective

Arjun Gupta *(pictured)* takes a different approach to advancing care. Rather than studying new anticancer treatments in the laboratory or clinic, he studies

patient access to therapy, rarely considered hidden costs, and burdens that impact quality of life during treatment and beyond. He is exploring ways to reduce "financial toxicity," including added out-of-pocket costs. For example, he says, a month's supply of pancreatic enzyme replacement therapy, to replace essential digestive enzymes the pancreas cannot make on its own, can cost upward of $1,000. Parking fees during the course of treatment can total hundreds of dollars and are not covered by insurance companies. These costs can accumulate and be a major burden for patients and caregivers. In a study of patients receiving radiation therapy to relieve pain caused by cancers that spread to the bone, Gupta found that many patients received 20 treatments, but the same pain control was achievable with just one treatment. The added inconvenience and expense of travel and time spent in waiting rooms are among the burdens that overuse of therapies place on patients, Gupta says. Under the mentorship of **Daniel Laheru**, he is leading a clinical study to assess the neuropathic, or nerve damage, component of pancreatic cancer pain using bedside testing, as well as treatment of the pain using a commonly available medication. This approach has the potential to redefine treatment of pancreatic cancer pain and reduce the use of unnecessary procedures, such as nerve blocks, and medications, such as opioids, he says. Finally, Gupta is focused on making sure patients have an opportunity to make fully informed treatment decisions. When given the choice, he says, patients overwhelmingly prefer home to being in the hospital. He is determining the proportion of time that patients receiving standard treatment for pancreatic cancer spend at home versus in rehabilitation or other care facilities.

Epigenetics Augments Immunotherapy

A native of Italy, **Marina Baretti** *(pictured)* believes her destiny is

to pursue clinical translational cancer research on a global scale. She has been working with pancreatic cancer experts **Elizabeth Jaffee** and **Nilofer Azad** to better understand the tumor microenvironment of pancreatic cancers and to look for novel immunotherapy treatments. In the lab, Baretti explores the effects of a histone deacetylase (HDAC) inhibitor called entinostat. This epigenetic drug controls gene expression without changing the DNA sequence. In a mouse model of pancreatic cancer, animals given the drug had an increase in the infiltration of immune system T cells and a decrease in the number and function of immune-suppressive cells. When given the drug together with a checkpoint inhibitor, the mice had a significant improvement in survival and delay in tumor growth. In the clinic, Baretti directed the first phase II study of combination epigenetic therapy and immunotherapy in patients with advanced pancreatic cancers and for whom standard chemotherapy failed. She analyzed results to look for any biomarkers to predict which patients were most likely to respond to the combination therapy, and why other patients may not respond, and what can be done to make their cancers more sensitive to the treatment.

Overcoming Treatment Resistance

Combination chemotherapy has led

to an improvement in overall survival for patients with metastatic pancreatic cancer, but due to the emergence of resistance mutations and the immunosuppressive nature of the pancreatic tumor environment, responses are not sustained. The goal of **Parul Agarwal** *(pictured)* is to overcome resistance. "Our ultimate goal is to evaluate and overcome mechanisms of chemotherapy and immunotherapy resistance in metastatic pancreatic cancer by using novel combinations of chemotherapy, immunotherapy and targeted agents," she says. Working with pancreatic cancer experts **Daniel Laheru** and **Dung Le**, Agarwal is exploring a novel strategy to optimize efficacy and minimize toxicity of regimens for metastatic pancreatic cancer. An ongoing phase II study is evaluating multi-agent, low-dose chemotherapy with gemcitabine, nab-paclitaxel, capecitabine, cisplatin and irinotecan in patients with metastatic pancreatic cancer. In an upcoming study, patients stabilized with this multiagent, low-dose chemotherapy would be candidates to receive maintenance therapy with combination immunotherapy and a poly (ADP-ribose) polymerase (PARP) inhibitor with the goal of achieving a more durable response. Related work will focus on evaluating biomarkers in blood and tissue samples from study participants to better characterize mechanisms of resistance.

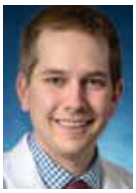
Making Immune Therapies Work Better

In an attempt to trigger a stronger response to immunotherapy in

pancreatic cancers, **Thatcher Heumann** *(pictured)* is working with **Nilofer Azad** and **Neeha Zaidi** to see if it might be possible to develop personalized pancreatic cancer vaccines and test them in combination with standard immunotherapy agents. Studying tumor samples from patients with stage 4 pancreatic and colon cancers, Heumann is looking for specific genetic mutations unique to these cancers that can trigger a strong antitumor response from the immune system. These neoantigens could then be used as the basis for novel vaccines against pancreatic cancer. These vaccines also would include a synthetic molecule called polyinosinic-polycytidylic acid (Poly-ICLC) used to improve the chances of stimulating the immune system to hunt when presented with the scent of these cancer neoantigens. They plan to study the vaccine, which will be given with checkpoint blocker immunotherapy. He says the vaccine plus immunotherapy could result in a more durable, robust immune response, hopefully translating into improved disease control and survival.

Effects of Aging on Pancreatic Cancer

How can aging affect the



microenvironment of pancreatic cancers? **Daniel Zabransky** *(pictured)* is exploring how aging affects the microenvironment of pancreatic cancer, or the cells in and around tumors. Working with pancreatic cancer expert **Elizabeth Jaffee** and cancer invasion and metastasis expert **Ashani Weeraratna**, Zabransky is evaluating the effects of aging on gene and protein expression and signaling activation in the pancreatic cancer tumor microenvironment, hoping to discover new pathways and molecular mechanisms that can be targeted for the treatment of pancreatic cancer. "We know from studies in melanoma that the age of the cells, particularly fibroblasts and immune cells in and around the tumor, affects nonmalignant cells, and the age of the patient seems to really affect how they behave and how the tumor then responds," Zabransky says. The goal of the project is to look at both younger and older patients and see how the ages of the cells in those microenvironments affect tumor growth and spread. The researchers think there are some differences in the way that they express genes or things that they secrete that change how the cancer cells grow and the immune system response to cancer. If they can find new pathways based on age, Zabranksy says, they potentially can come up with new treatment strategies that can be better tailored to patients based on what actually is going on in their bodies.

ADVANCES

Discoveries in Cancer Medicine

Treating Cancer while Protecting Healthy Organs

As a radiation oncologist who specializes in pancreatic cancer, **Amol Narang** has the unique challenge of treating a cancer that is surrounded by radiation-sensitive organs and tissue.


Narang

"It's generally important to deliver a high amount of radiation to the tumor to achieve a good outcome," says Narang, "but for the pancreas, it's difficult because the duodenum (the part of the small intestine that surrounds and connects to the head of the pancreas) and stomach are intimately close to the pancreas." Protecting these organs means limiting the dose of radiation that could be given to the tumor, he explains. That is changing, however, with a new product called hydrogel. The spacer gel, which has toothpastelike consistency, provides a biodegradable cushion between the pancreas and surrounding organs during radiation treatment.

Narang is working with radiation physicist **Kai Ding,** gastroenterologist **Eun Ji Shin**, and collaborators at Harvard and MD Anderson Cancer Center to study the spacer gel, which is injected through endoscopy-guided ultrasound and disappears from the body in a few months.


Ding

By the time of diagnosis, many pancreatic cancers have broken through the wall of the pancreas and attached to nearby blood vessels. In these "locally advanced" pancreatic cancers, radiation therapy can decrease the size of the tumor, pull it away from the nearby blood vessels and make full removal of the tumor by surgery possible, reducing the chances of the cancer coming back. "This extra space the hydrogel provides may allow for the higher dose we need to destroy the tumor and may minimize the dose to other nearby organs we want to protect," Narang says.

He is also studying drugs known as radioprotectors that can be given before or after radiation treatment, allowing higher doses of radiation to be delivered while neutralizing its effect on healthy organs and tissue.

Combating Liver Cancer

Liver cancer is one of the fastest-growing causes of cancer death in the U.S. and in many other parts of the world, says **Mark Yarchoan**, co-director of the Liver Cancer Multidisciplinary Clinic. Since the new liver cancer clinic launched a little more than a year ago, they have seen a more than 500% increase in patient volume. A team of Johns Hopkins medical oncologists, interventional radiologists, radiation oncologists, surgeons, radiologists, pathologists, palliative care specialists and research nurses are collaborating to change the trajectory of liver cancers through pioneering laboratory and clinical research.


Yarchoan

Fibrolamellar hepatocellular carcinoma (FLC), a very rare form of liver cancer that usually affects children and young adults and has no standard treatment, is an active area of clinical research, Yarchoan says. He and colleague **Marina Baretti** developed a vaccine that may help the body's immune system recognize FLC tumors. They are studying the use of this new vaccine in combination with two other immunotherapies, nivolumab and ipilimumab. This will be the first clinical trial to specifically target the gene that drives FLC, he says.

Nilofer Azad, co-director of the clinic, and Yarchoan are working together on a national trial that studies the drugs cobimetinib, a MEK inhibitor, in combination with the immunotherapy atezolizumab in bile duct cancer (also called cholangiocarcinoma). The initial results, which demonstrated that the combination delayed tumor progression as compared with atezolizumab alone, were presented at this year's annual meeting of the American Association for Cancer Research.

MEK inhibitors may make immunotherapies work better through an interaction among cancer cells and immune cells, but work on preclinical models and on clinical samples from the trial suggest that MEK inhibition may cut both ways, Yarchoan explains. MEK inhibitors increase the number of immune cells in the tumor, but they also make these immune cells less active. His laboratory is studying whether the addition of other immunotherapies could rescue T cell activation and make this treatment combination work better.

The Liver Cancer Multidisciplinary Clinic is also pioneering a new approach to treating hepatocellular carcinoma (HCC), the most common form of liver cancer. A curative surgery is the ideal treatment but often not an option, Yarchoan says. Most liver cancers recur after surgery, he says.

In a new approach, Yarchoan and collaborators are using a combination of targeted therapy and immunotherapy to try to shrink liver cancers, potentially allowing patients with locally advanced or inoperable cancers to eventually undergo surgery and reduce the chances that these cancers come back. This treatment approach of immunotherapy before surgery was pioneered at the Kimmel Cancer Center for lung cancer with results so promising that it is being studied in several other cancer types. By the time of surgery, many patients see their tumors disappear or significantly diminished in size.

New Advances in Therapies

Five-Drug Combo

Patient Arnold's advanced pancreatic cancer that had spread to his liver was eliminated with a low-dose, five-drug combination being studied in a clinical trial led by **Dung Le**.


Le

Le is testing new iterations of the therapy to see if she can help more patients. A new drug cocktail adds immunotherapy and a PARP inhibitor to the mix. Immunotherapies are aimed at unleashing the body's natural defense against foreign invaders, including cancer. PARP inhibitors are called targeted therapies because they block enzymes that help cancer cells repair DNA damage caused by radiation therapy and chemotherapy. Such DNA damage also makes cancer cells more visible to the immune system.

Le and colleagues believe one reason Arnold's cancer responded well to the therapy was because it contained a BRCA mutation, at once predisposing him to cancer and, with this therapy, becoming the cancer's Achilles' heel. BRCA genes act as DNA repair mediators. Using a PARP inhibitor in patients with other DNA repair defects may have similar effects and could have immune stimulatory effects in other patients as well.

Michael Pishvaian and **Katie Bever** are looking more deeply into the PARP/BRCA DNA repair mechanisms and how they affect responses to treatment. They wonder if adding a PARP inhibitor to therapies in patients who have BRCA mutations augments responses. A subset of patients with BRCA mutations have good responses to treatment, but in many others, the mutation has no effect. Some research studies showed that inhibiting PARP can make unresponsive tumors respond to immunotherapy. Pishvaian and Bever want to see if PARP inhibitors may do the same thing for patients with BRCA mutations whose cancers are resistant to treatment.


Bever

"PARP is another way cancer cells make repairs," says Le. "If we block it, they can't make repairs and they die." Targeting more than one repair mechanism may expand responses to more patients.

From the molecular standpoint, they can't find evidence that tells them why one patient with a BRCA mutation responds to treatment and another does not. **Nilofer Azad**, gastrointestinal cancer expert and Cancer Genetics and Epigenetics Program co-director, is exploring whether immune cells called macrophages could be playing a role. Macrophages are linked to inflammation, which alone are cancer-promoting, but it may also be turning away cancer-fighting T cells. The drug etinostat is being studied for its ability to target macrophages and create a T cell-friendlier environment.

A series of studies is combining the listeria vaccine — which uses a weakened version of the bacterium listeria safe for humans — to stimulate an immune response in combination with different immune checkpoint-blocking drugs. Checkpoint blockers target the on/off signals of the immune system, which are often hijacked by cancer cells, to release the brakes on the immune response to cancer. One combination involves a new checkpoint, called CXCR4, which clears the way for more T cells to traffic to the tumor. Other combinations include PD-1 and IDO blockers. The researchers will study tissue samples to see what immune cells are showing up and if targeting macrophages improves the immune system's ability to attack the cancer.

This research is being led by **Bever** and is funded by the Lustgarten Foundation, Swim Across America and the Cynthia Boscov Fund.

Three Scientists Named to Exclusive Research Network

Three Convergence Institute scientists were among the first 45 members selected to join the 10x Genomics Visium Clinical Translational Research Network (CTRN), aimed at advancing translational research in some of the world's leading health problems, including oncology, immuno-oncology, neuroscience, infectious disease, inflammation and fibrosis, and COVID-19.

Elizabeth Jaffee, M.D., the Dana and Albert "Cubby" Broccoli Professor of Oncology and deputy director of the Kimmel Cancer Center, **Elana Fertig, Ph.D.**, associate professor of oncology, biomedical engineering, and applied mathematics and statistics, and director of Quantitative Sciences, and **Luciane Kagohara, Ph.D.**, instructor in oncology, will partner in this new collaborative network. Jaffee is director, Fertig is co-director and Kagohara is a member of the Convergence Institute at the Johns Hopkins Kimmel Cancer Center.

They will focus on advancing spatial gene expression technology and explore immunotherapy in gastrointestinal cancers, including liver and pancreatic cancers. They will use single cell and spatial technologies — a new but rapidly advancing field of cancer study — on tumor samples from patients participating in clinical trials to understand the effect immunotherapies have on tumor cell and immune cell populations.

The researchers also expect to uncover biomarkers of response that will guide therapy, from immunotherapies aimed at immune checkpoints that will release restraints on the immune system to the addition of targeted drug therapies that could work in combination to break through cancer's resistance to treatment. ▶▶

"The 10x Genomics Visium Clinical Translational Research Network gives us the opportunity to expand these collaborations to a global scale," says Fertig. "These technologies and added fields help us understand how tumors respond to therapy in a new way."

Robotic Surgery an Option for Patients with Pancreatic Cancer

The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care has one of the country's busiest pancreatic surgery practices. It is also one of just a few centers in the U.S. that offers a unique type of surgery: robotic surgery.

For many patients, this specialized type of surgery has advantages over traditional open operations. A much smaller incision results in more rapid recovery, allowing patients to proceed to complementary treatments with drug therapies and radiation therapy up to two weeks sooner.

"Most pancreatic cancers require some combination of treatments that include surgery, chemotherapy, radiation therapy and/or immunotherapy. Robotic surgery reduces complications, speeds up recovery and gets patients to other therapies more quickly," says **Jin He**, the Paul K. Neumann Professor of Pancreatic Surgery.


He

Robotic surgery can also offer better access to hard-to-reach areas, enhancing dexterity and improving view of the surgical field compared to laparoscopic surgery. For patients, this can result in more precise procedures, less risk of wound infection and blood loss, and a quicker return to regular daily activities, explains He.

As part of the Skip Viragh Center's multispecialty team, He performs open and robotic Whipple procedures, a kind of pancreatic surgery perfected at Johns Hopkins (it is also called a pancreaticoduodenectomy). During the procedure, which is the primary surgical treatment for many pancreatic cancers, surgeons remove the head — and sometimes the body — of the pancreas, a part of the small intestine called the duodenum, a portion of the bile duct, the gallbladder, associated lymph nodes and sometimes a small portion of the stomach.


Jin He, M.D., Ph.D. (left) with Matthew Weiss, M.D.

Johns Hopkins was an early adopter of robotic technology, and it has advanced significantly over the last decade, facilitating more complicated surgeries.

"We couldn't have done a robotic Whipple procedure 10 years ago," He says. "New technology and equipment make it possible now."

Of particular interest to He is the advantage of robotic procedures for patients with precancerous pancreatic cysts called IPMNs (intraductal papillary mucinous neoplasms) and pancreatic neuroendocrine tumors. In some patients, these benign neoplasms can either progress to cancer or spread to other organs and must be surgically removed.

"These patients are often younger and have no symptoms, and we can use robotic surgery to get the tumor out less invasively and with fewer complications and a shorter recovery, getting patients back to their lives sooner," says He.

FOR YOUNGER PATIENTS, THIS CAN RESULT IN MORE PRECISE PROCEDURES, LESS RISK OF WOUND INFECTION AND BLOOD LOSS, AND A QUICKER RETURN TO REGULAR DAILY ACTIVITIES.

For patients with advanced pancreatic cancers and major blood vessel involvement, open surgeries remain the best strategy, says He. For most patients, however, he says, robotic surgery is an option, one many patients come to the Skip Viragh Center seeking.

SUCCESS STORIES

A Voice of Hope

For patients and family members reeling from a new diagnosis or the effects of pancreatic cancer, senior research nurse **Susan Sartorius-Mergenthaler** *(pictured)* is often a voice of hope, comfort and guidance.

"Senior" seems an inadequate way of describing Sartorius-Mergenthaler's decades of experience. She came to the Cancer Center in 1984 as a nurse on the inpatient unit for patients with solid tumors. Throughout her career, she also worked as a research nurse and nurse educator.

For the last five years, she been the clinical trials referral nurse for patients with gastrointestinal cancer. She is the person patients and family members turn to in their most unfathomable moments — when they learn they have cancer, that their cancer has come back or worse: a treatment that was working stopped working. She answers their questions and guides them to clinical trials of promising new treatments.

She talks to more than 100 doctors, patients and family members from across the country and around the world each month. Many of the patients who call Sartorius-Mergenthaler are desperate. Their cancers are advanced. They are scared. Many were told there is no hope for them.

"Our cancer center has become known all over the world for treatment of pancreatic cancer. Patients hear something on the news or search the internet and find us, and they call," says Sartorius-Mergenthaler.

She reviews their records, searching through their medical history, pathology, imaging reports and lab work to match them to a clinical trials — investigative studies of promising new therapies — that might work against their cancer. The drugs and treatment schedules are often complicated, but Sartorius-Mergenthaler explains each step. Her lengthy experience is reassuring to patients. She has seen much progress throughout her 36 years at the Kimmel Cancer Center, witnessing firsthand the successes of clinical trials and patients who recover against all odds.

"These people are our motivation," she says. "They have unimaginable strength and courage, and they are magnanimous. They want to participate in something that they cannot be sure will help them and often talk about how they may be able to help the next patient. They are so positive and hopeful."

Sartorius-Mergenthaler has seen many success stories during her years at the Kimmel Cancer Center. She recalls the phase I clinical trials of the chemotherapy drugs taxol, taxotere and irinotecan in the late 1980s and early 1990s. As a research nurse, she was part of a small group of physicians and nurses who first gave these drugs to patients, developing the clinical trials to study their effectiveness against cancer and how best to manage side effects. She traveled around the country educating other caregivers about the drugs. Today, all of the drugs are standard treatments for many types of cancer.

"That is the hope and power of collaborative research," she says. "Together, we moved laboratory research to patients."

> "TOGETHER, WE MOVED LABORATORY RESEARCH TO PATIENTS."

More recently, before taking on the role of clinical trial referral nurse, she was a research nurse working with melanoma skin cancer patients, including those on clinical trials of a vaccine aimed at boosting the immune attack against the cancer.

"When I was a new nurse, many diagnosed with melanoma died," recalls Sartorius-Mergenthaler. "Now, with immunotherapy, there are patients who have active metastatic melanoma but who are getting long-term responses. It's extraordinary."

From her office window in the Skip Viragh Outpatient Cancer Building, Sartorius-Mergenthaler can see the Kimmel Cancer Center's Weinberg Building and its two cancer research buildings. They are a physical representation of the great growth and advances against cancer.

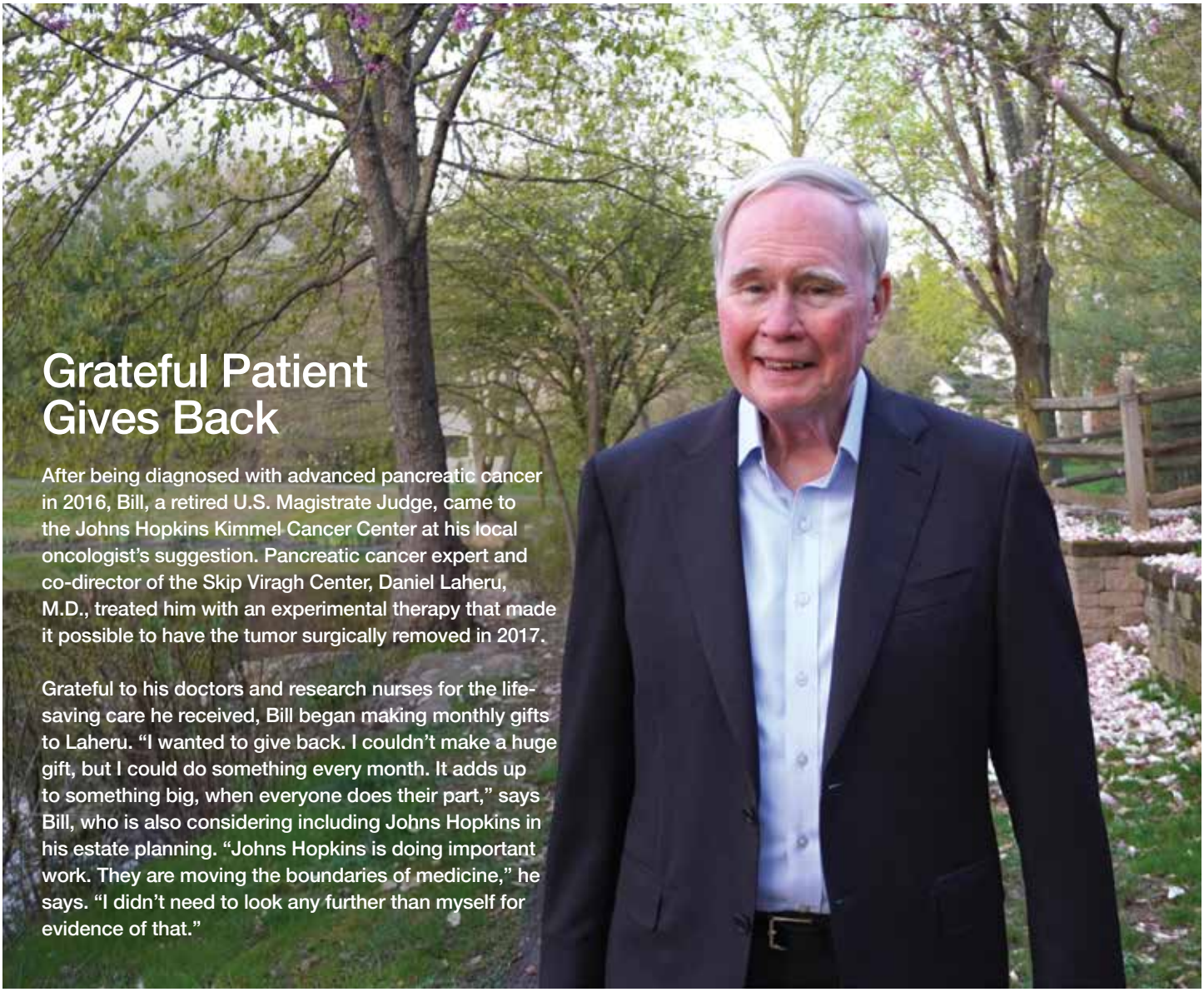
"In 1976, we had one building for treatment and research," she recalls. "Now we have the largest footprint at Johns Hopkins."

She says the Convergence Institute is another example of progress. "The science is incredible. We are taking everything we've learned and applying new technologies and ideas, looking at cancer from different angles and bringing in people with different areas of expertise. It's really extraordinary," says Sartorius-Mergenthaler.

As many patients as she has helped over her 30-plus years, she believes she's gained more than she's given. This kind of experience is key because there is no rule book, no step-by-step system that is right for each patient. She listens, learns and responds to each patient's needs.

There is something special about working with cancer patients, she says. The growing science and new medicines that have changed the landscape of the disease are part of it, but even more compelling, she says, is the emotional impact of what they do in helping people through one of the most difficult times of their lives.

"I've spent my whole career in this cancer center. The opportunities to grow as a nurse have been wonderful. I work with the best of the best," she says. "It's an honor to be able to talk to patients and answer their questions. I love what I do. I can't imagine doing anything else."



Grateful Patient Gives Back

After being diagnosed with advanced pancreatic cancer in 2016, Bill, a retired U.S. Magistrate Judge, came to the Johns Hopkins Kimmel Cancer Center at his local oncologist's suggestion. Pancreatic cancer expert and co-director of the Skip Viragh Center, Daniel Laheru, M.D., treated him with an experimental therapy that made it possible to have the tumor surgically removed in 2017.

Grateful to his doctors and research nurses for the life-saving care he received, Bill began making monthly gifts to Laheru. "I wanted to give back. I couldn't make a huge gift, but I could do something every month. It adds up to something big, when everyone does their part," says Bill, who is also considering including Johns Hopkins in his estate planning. "Johns Hopkins is doing important work. They are moving the boundaries of medicine," he says. "I didn't need to look any further than myself for evidence of that."

Help Us Make a Difference

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

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

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