2 Decades of Immunology Research Pays Off

Many new opportunities to pursue

Elizabeth Jaffee has devoted her entire career to figuring out how to engage the immune system against cancer, particularly pancreatic cancer. Her work led to the first therapeutic cancer vaccine, known as GVAX. It recruited vital immune killer T cells to pancreatic tumors in force. This in and of itself was a victory because historically, pancreatic cancers did not attract the attention of the immune system.

In April 1997, Jaffee and colleagues reported that GVAX awakened the immune system. It occurred in an environment of promising findings that were frequently dashed in the clinic. The vaccine approach—developed almost a decade earlier by Jaffee, Drew Pardoll and Hyam Levitsky—was a rare immunology success story. It proved that the immune system could be coaxed to mobilize against cancer.

Jaffee and colleagues’ vaccine had overcome a major barrier, and these cells—manufactured by our own body and immensely more powerful than any anticancer drug—were preventing the T cells from doing their job.

It took another decade for Jaffee and colleagues now realized that it wasn’t cancer’s ability to suppress immune cell recognition of the cancer. They would also have to disrupt cancer’s ability to suppress the immune system. This relentless determination paid off. The discovery that cancer cells were corrupting this natural regulatory process used to shut down the immune response when its job was done created a new paradigm.

The process was dubbed immune tolerance. Jaffee and her immunology colleagues now realized that it wasn’t enough to get the immune system to recognize the cancer. They would also have to disrupt cancer’s ability to suppress the immune system.

Jaffee and colleagues stayed the course, convinced that, in time, they would unlock the clues that could make the immune system the perfect weapon to fight cancer. Jaffee and Laheru recruited the best and brightest minds. Laheru led the clinical research, and young investigators Dung Le, Eric Lutz and Lei Zheng helped Jaffee make progress.

Immune cells were being duped. They were essentially being told, ‘Go home. There is nothing to see here,’” says pathologist Bob Anders.

“The process was dubbed immune tolerance. Jaffee and her immunology colleagues now realized that it wasn’t enough to get the immune system to recognize the cancer. They would also have to disrupt cancer’s ability to suppress the immune system.

Jaffee’s body of work earned her superstar status in the world of cancer immunology and pancreatic cancer research. She is an associate director of the new Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, formed last March to speed the translation of cancer immunology discoveries into new therapies. She was chosen to lead the Stand Up To Cancer-Lustgarten Foundation Pancreatic Cancer Convergence Dream Team to transform pancreatic cancer into a treatable disease. She was also honored with the 20th annual American Association for Cancer Research Joseph H. Burchenal Award for Outstanding Achievement in Clinical Cancer Research for her basic science and clinical contributions to...
They are working to do more work to make the

4 more work to do. They are working to in a better way,” says Margaret Tempero, attempted to do it, but the Kimmel cancer research and treatment. “Everyone called—more than 60 a month—for worldwide attention, and patients out of the Jaffee laboratory attracted and news of promising research coming the chance they gave me.”

“I am thankful for cancer,” says Bender. “I have only months to live when their cancers a 20-year survivor, and Donna Bender, Jaffee’s pancreatic cancer vaccine offered forms of cancer and one for which few cancer—one of the most dreaded癌症 immunology. Her most recent accolade was her selection by Vice President Joe Biden as co-chair of his Cancer Moonshot Blue Ribbon Panel. She was the obvious choice, as Jaffee had already created the model Vice President Biden envisioned for his moonshot, one that reflected cooperation among academia, government, the private sector and philanthropy to translate cancer immunology research into new therapies for patients. To bring cancer vaccines to patients, Jaffee became an expert in FDA regulations and vaccine manufacturing, opening a Good Manufacturing Practices facility at the Kimmel Cancer Center to make the vaccine. Jaffee’s laboratory was a beacon of hope for those diagnosed with pancreatic cancer—one of the most dreaded forms of cancer and one for which few therapeutic advances had been the Whipple procedure, the primary—and potentially curative—surgical treatment for pancreatic cancer, was also perfected at Johns Hopkins. For patients who could not be cured with surgery, however, Jaffee’s pancreatic cancer vaccine offered the possibility that one day cancer in check. Patients like Kathleen Dowell, now a 20-year survivor, and Donna Bender, a 12-year survivor, sought out Jaffee and Laheru after being told they had only months to live when their cancers progressed after surgery, chemotherapy and radiation therapy. “Dr. Laheru and my nurse, Beth Onners, were as determined as I was to take on this cancer,” says Bender. “I am thankful for the chance they gave me.”

This type of response was unheard of before the GVAX vaccine. These results and news of promising research coming out of the Jaffe laboratory attracted worldwide attention, and patients called—more than 60 a month—for appointments at the Kimmel Cancer Center. “There is no other cancer center doing this kind of work,” says Zheng. It earned the Kimmel Cancer Center the reputation as the leader in pancreatic cancer research and treatment. “Everyone attempted to do it, but the Kimmel Cancer Center was able to accomplish it in a better way,” says Margaret Tempreno, director of the University of California San Francisco Pancreas Cancer Program. Despite the accolades and reputation, Jaffee and Laheru recognize there is much more work to do. They are working to improve immune therapies for pancreatic cancer and extend the benefit to many more patients.

The Viragh Difference One of those patients who sought the expertise of Jaffee and Laheru was Skip Viragh. Viragh was a mutual fund investment leader whose life was cut short in 2003 by pancreatic cancer. Before his death, Viragh established the Viragh Family Foundation and cemented his mission to ensure a better future for patients fighting pancreatic cancer. A $20 million initial investment in 2009 established the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. The Skip Viragh Center allowed the Kimmel Cancer Center to accelerate clinical research, expand the number of patients treated and, through Viragh-funded scholarships, increase the number of scientists dedicated to the understanding and treatment of pancreatic cancer. The Skip Viragh Center rapidly became the worldwide model for how to combat the disease.

“The Skip Viragh Center and Viragh Scholars program, established through Skip’s profound generosity, have made the Kimmel Cancer Center a powerhouse in developing new treatments for pancreatic cancer,” says Laheru. “We are able to recruit and retain the best pancreatic cancer scientists, realize revolutionary laboratory and clinical advances, and provide unparalleled care to patients.”

The influx of patients that came from these discoveries and the creation of the Skip Viragh Center transformed cancer care, creating a clinic model that brought together experts from every discipline involved in treating pancreatic cancer. Experts from around the world and the country come to the Kimmel Cancer Center to learn what makes the Skip Viragh Center so unique. “We cannot overstate the importance and impact that Skip has made—and continues to make—on pancreatic cancer research and treatment,” says Jaffee. “It allowed us to integrate the basic science and clinical expertise to provide the best and most innovative care to patients.”

With Viragh funding, Jaffee and Laheru hired nurse practitioner and immune therapy expert Barbara Biedrzycki to oversee patient care. “She was one of the best nursing leaders in the world, and she has played a vital role in increasing the patient volume in our clinic, particularly patients with advanced pancreatic cancer who have very few treatment options,” says Laheru.

Since opening, the clinic has seen more than 2,000 pancreatic cancer patients. It continues to expand and will move to the new Skip Viragh Outpatient Cancer Building upon its completion in the fall of 2017 (see story on page 14). This new facility is funded entirely by private donations, including a $65 million gift from Viragh’s foundation, and offers the potential to double the number of patients the clinic can see each day. The latest immune therapy discoveries are being made to patient care in the most advanced clinical setting. “Skip’s generosity allowed us to build this premier program. Now, we must embark on the next phase, using the tools we’ve created and discoveries we have seen,” says Jaffee. “I am last to help even more patients,” says Laheru. “This can only be accomplished with additional research.”

Expanding Research In 2016, another patient of Laheru’s made a gift to advance pancreatic cancer research. Linda Rubin, 65, lost her life to the cancer this year, and like Viragh, she believed so strongly in the work of Laheru and Jaffee that she established the Linda Rubin Family Fellowship in Pancreatic Cancer Research and Patient Care. “As a former teacher and practicing veterinarian for 35 years, I have had the opportunity to both learn from and teach to and mentor talented people. Education is the future, and I want to be a part of that future in any way I can,” said Rubin. “The best we can hope for is that intelligence, novel thinking and focused determination will lead the way out of the dark world of cancer into the bright world of survival.”

Mark Yarchin was selected as the inaugural Linda Rubin Fellow. Jaffee and Laheru will mentor him as he explores the benefit of combining immunotherapies and, specifically, whether the addition of immune checkpoint inhibitors can increase the effectiveness of the pancreatic cancer vaccine.

“The opportunity for aspiring investigators to work with senior faculty members at the Kimmel Cancer Center has allowed our program to consistently attract the most gifted young physicians-scientists from around the globe,” says Laheru. “The best way we can honor Linda is to develop better treatments for pancreatic cancer, and the fellowship she established makes that possible.”

Young Investigators “The progress we’ve made—which has only been possible because of the generosity of others—helps us attract and keep the best and brightest young clinicians and scientists,” says Jaffee. “Our young scientists are essential to continuing discovery.”

Le, the first Viragh Scholar, played a leading role in identifying a mismatch repair alteration known as mismatch repair as a critical biomarker for response to an immune therapy, called checkpoint blockade.

Immune checkpoints are one of the main mechanisms cancer cells use to suppress an immune response. The large numbers of mutations common to mismatch repair alterations serve as an alert to immune cells because they make the tumor look very different from normal cells. “For other treatments, including chemotherapy, the changing tumor biology due to accumulating mutations causes treatments to stop working, but it seems to make immune therapies work better,” says Le.

Some of the early responses in a clinical trial of 48 patients were so dramatic that they were highlighted at the 2016 New England Journal of Medicine and at the 2015 and 2016 American Society of Clinical Oncology annual meetings. The FDA breakthrough status for immune therapy with the checkpoint blockade nivolumab in patients with mismatch repair deficiency.

Stefanie Johno, 25, was one of the patients who participated in the clinical trial. She was near death, battling an aggressive hereditary colon cancer that did not respond to surgery or chemotherapy. Out of options and in excruciating pain, she searched desperately for other
When Joseph Edens began experiencing abdominal pain, he knew something wasn’t right, but he didn’t expect to learn he had pancreatic cancer. “The worst thing I could have thought of happened,” he says of the diagnosis. His mind immediately turned to his wife and two children. He did his research. He knew the survival statistics, but he was determined to beat the cancer. “We looked nationwide and worldwide for the best place for pancreatic cancer, and that turned out to be Johns Hopkins,” he says. Edens’ cancer was treated by Christopher Wolfgang and medical oncologist Lei Zheng, but many specialists collaborated to prevent the cancer from recurring and to manage the digestive changes that result when the pancreas is removed. “This is an example of the multispecialty care provided at the Kimmel Cancer Center. Experts in surgery, oncology, gastroenterology and endocrinology all participated in Mr. Edens’ care,” says Zheng. Six years later, he remains cancer-free.

Other variations include combined treatments. In some patients, giving the immune-modulating drug cyclophosphamide before the vaccine causes immune structures to form inside tumors that help regulate immune cell activation. “These organized immune structures do not naturally appear in pancreatic cancers,” says Jaffee. “This suggests that there has been significant reprogramming of immune cells within the tumor.” There is evidence that adding a checkpoint blockade treatment to the mix could further enhance immune activity.

Another combined approach adds a second kind of vaccine, a weakened version of the bacterium Listeria. The Listeria is genetically modified to be safe for humans but stimulates an immune response against the protein mesothelin. Jaffee and Le believe the protein helps pancreatic cancer cells to grow and spread. “The combination essentially trains the immune system to recognize and attack pancreatic tumors,” says Jaffee. “Private support has become essential to the progress of research.”

The benefit of research is undeniable as new opportunities to improve pancreatic cancer treatment abound at the Kimmel Cancer Center. Long-Lasting Responses Gene Ogle is an example of someone whose cancer continues to respond to immune therapy. He benefited from research that showed that giving the vaccine before surgery could help many patients. When Ogle’s doctor told him he had pancreatic cancer, his first question was: “How long do I have to live?” He was just 54 years old when he got the news, and his thoughts immediately turned to his father, who died of the same disease 30 years earlier, at 63. Although many years had passed, his memory was clear. “My father died two months after he was diagnosed. My knowledge was that it was incurable and killed quickly.”

Ogle’s doctor told him that there had been many advances since his father’s diagnosis and specifically referred to discoveries at the Kimmel Cancer Center. He decided to make an appointment at its Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. Despite the diagnosis, there was some good news. His cancer was not as advanced as his father’s, and he was a candidate for a Whipple procedure, a complex pancreatic cancer surgery perfected at Johns Hopkins. At the appointment, research nurse Carol Judkins also talked to him about a clinical trial testing the value of giving a pancreatic cancer vaccine before surgery. The pancreatic vaccine could supercharge his immune system, drawing cancer-attacking killer T cells to pancreatic tumors. Jaffee and Laheru had laboratory evidence that giving the vaccine before surgery gave the immune system a step up on the cancer and might help it get at microscopic cancer cells that could cause the cancer to spread. She was working with Le and Zheng to explore whether earlier use of the vaccine would provide a clinical advantage.

Ogle was well aware of the high rate of pancreatic cancer spread and recurrence. As an engineer, he is a numbers guy. He recalled a survival chart he saw around the time of his surgery. “It peaked at one year and went down after that. Less than 5 percent of people survived past five years,” says Ogle. “Enrolling in the vaccine trial was an easy decision for me,” says Ogle. “I still had no hope that I would survive, but I thought if I participated in the vaccine...
study, I might be able to help doctors move that survival curve far beyond 5 percent.”

That was nearly six years ago, and contrary to the statistics and his own personal predictions, Ogle is alive and doing well. It’s been almost four years since his final vaccination. His cancer isn’t gone, but it’s not growing. With the boost from the vaccine, his immune system appears to be keeping it in check. “I’m still here, and I want to be a message of hope to others,” he says.

Ogle fully expected to become a pancreatic statistic, but not a positive one. “My perspective is changing,” he says. He is certain the wonderful care he received, including surgery, chemotherapy, radiation therapy and particularly the pancreatic cancer vaccine, allowed him to beat the odds. “I’m so proud to be a part of these studies. It’s a huge honor,” says Ogle. “Everyone who took care of me—from the receptionist to the nurses and doctors—was top-notch. They all had so much compassion.”

Over the last six years, Ogle estimates that he’s made the 270-mile trip from his home in Roanoke, Virginia, to the Skip Viragh Center at least 100 times. There were other comprehensive cancer centers and some good community hospitals much closer to his home. In fact, many of his relatives and friends questioned his choice to travel so far. “I did my research before I made a decision, and Johns Hopkins came up on top,” says Ogle. “I have never regretted that decision—not one time.”

Ogle recently celebrated his 60th birthday, a milestone he never expected to reach. He is also spending time with his three grandchildren, two of whom were born after his diagnosis. “I am so thankful that I lived to see them. I didn’t think I would,” he says. “I’m beating this disease. That’s a message people need to hear.”

He wants everyone to understand the power and the value of research. “A lot of progress has been made, but there is still a long way to go,” he says. “That’s the only way we’re going to permanently move that survival curve.”

Jaffee agrees. She says: “This is the type of progress I imagined three decades ago, when I first began studying the immune system. For the first time, I think the possibilities are really limitless.”

The Pancreatic Cancer Multidisciplinary Clinic is a one-day clinic that offers a complete, comprehensive examination, including imaging tests, such as CT scans, by some of the top cancer experts in the country. To make an appointment, call 410-933-PANC(7262).

PancMD Video Series The PancMD video series introduces you to the Johns Hopkins experts who gather their knowledge and expertise for patients in the Pancreatic Cancer Multidisciplinary Clinic, including Daniel Laheru and Barbara Bedrosyan. Topics include medical oncology, nutrition, radiology, surgery, genetics, and clinical trials. Watch the videos at http://bit.ly/pancvideos.

Elizabeth Jaffee

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—ELIZABETH JAFFEE

Jaffee Appointed to National Cancer Leadership Initiatives

Elizabeth Jaffee, co-chair of the Cancer Moonshot Blue Ribbon Panel, speaks at a White House press briefing. Jaffee is deputy director of the Kimmel Cancer Center, co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, and associate director of the Bloomberg–Kimmel Institute for Cancer Immunotherapy.

“‘The science is here. The time is right. Our field is energized. We hope this will turn into therapies that can potentially cure patients with metastatic disease. I truthfully believe it will lead to better outcomes.’”

Cancer Moonshot Initiative

The 21st Century Cures Act received nearly unanimous approval by the U.S. Senate. The bill includes $4.8 billion in new funding for the National Institutes of Health, including $1.8 billion for the National Cancer Moonshot initiative, championed by Vice President Joe Biden and aimed at solving cancer’s greatest challenges. Elizabeth Jaffee was selected as co-chair of the Cancer Moonshot Blue Ribbon Panel and also serves as co-chair of the initiative’s Immunology Working Group.

Jaffee is charged with helping to set the direction for the Cancer Moonshot and recently announced recommendations at a White House press briefing for speeding the pace of cancer discovery.

10 Years of Progress in 5 Blue Ribbon Panel Recommendations

- Establish a network for direct patient involvement in cancer research.
- Create a translational science network devoted exclusively to immunotherapy.
- Develop ways to overcome resistance to therapy.
- Build a national cancer data ecosystem.

Read the Blue Ribbon Panel Report at cancer.gov/brp. Watch a video: youtu.be/uQBNApEb1a8

Stand Up To Cancer

Elizabeth Jaffee is a team leader of the Stand Up To Cancer: The LungCancer Foundation Pancreatic Cancer Convergence Dream Team charged with bringing all specialties together to fight pancreatic cancer.

“We are focusing on how the immune system shapes cancer and how we can alter the immune system to fight it,” says Jaffee. “We believe the immune system has the power to ultimately defeat pancreatic cancer.”

Jaffee, an international leader in cancer immunology, has focused her career on understanding the biology of pancreatic cancer and how to use the immune system against it. “I believe we are on the verge of many good therapies that are not toxic and give patients a good quality of life,” says Jaffee, an associate director of the Bloomberg–Kimmel Institute for Cancer Immunotherapy. “This is a new era for using the immune system to fight cancer.”

The Kimmel Cancer Center’s Stephen Baylin, Elizabeth Jaffee, and William Nelson participated in the 2016 Stand Up To Cancer Telethon held last September.
25 Years of Cancer Immunology Discovery

1989
Cancer immunology researchers Elizabeth Jaffee, Drew Pardoll and Hyam Levitsky develop GVAX, the first therapeutic cancer vaccine. This work led to the development of pancreatic, prostate, kidney, breast and other cancer vaccines.

2000
Scientists discover the immune system-related molecules PD-L1 and PD-L2 on the surface of cancer cells. Known as immune checkpoints, they are found to partner with PD-1 to hide cancer cells from the immune system.

2001
Jaffee, Daniel Laheru and team conducted the first clinical studies of a pioneering therapeutic pancreatic cancer vaccine.

2005
Early results of GVAX are encouraging; it becomes one of the few new therapies to increase survival in some patients with pancreatic cancer.

2007
Clinical trials of experimental drugs that target and interfere with the PD-1 molecule begin.

2009
The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care opens, accelerating pancreatic cancer immune therapy advances.

2010
Johns Hopkins Kimmel Cancer Center scientists lead an early clinical trial of the experimental checkpoint blockade-targeting drug MDX-1106, now known as Bristol-Myers Squibb’s nivolumab (Opdivo).

2013
Science magazine calls cancer immunotherapy the Breakthrough of the Year and cites work by Kimmel Cancer Center scientists.

2014
Jaffee, Lei Zheng, Eric Lutz, Laheru and their Skip Viragh Center team developed and tested a vaccine that triggered the growth of immune cell nodules within pancreatic tumors, essentially reprogramming these intractable cancers and potentially making them vulnerable to immune-based therapies.

Researchers test a combination of the GVAX vaccine with a second one that contains a modified version of the bacterium Listeria in 90 pancreatic cancer patients.

2015
Viraj Scholar Dung Le leads a study of mistakes in so-called mismatch repair genes that accurately predict who will respond to certain immunotherapy drugs known as PD-1 inhibitors.

2016
Mismatch repair biomarker receives FDA breakthrough status.

BLOOMBERG-KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

With leading funding from Michael Bloomberg and Sidney Kimmel, the Bloomberg—Kimmel Institute for Cancer Immunotherapy is announced at Johns Hopkins. Vice President Joe Biden calls it a model for driving progress and the site of some of the next generation’s breakthroughs in cancer treatments.

Jaffee is named co-chair of the Vice President’s Cancer Moonshot Blue Ribbon Panel and chair of the National Cancer Advisory Board.
The Next Generation of Pancreatic Cancer Pioneers

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.

Hope For the Most Advanced Pancreatic Cancers

Katherine Bever is collaborating with Dung Le to bring hope to patients facing the most advanced form of pancreatic cancer. Bever and Le are developing clinical trials for patients with advanced pancreatic cancers that have spread outside of the pancreas. One immune therapy trial uses a pancreatic cancer vaccine GVAX to bring cancer-killing T cells to pancreatic tumors with immune checkpoint inhibitors to block PD-1 and IDO, that in many cancers act like an off-switch for T cells and shut down the immune response.

They plan to treat patients with PD-1 and IDO inhibitors and the GVAX vaccine followed by the listeria vaccine. Listeria bacteria augment the vaccine response and are engineered to express mesothelin, an immune cell-alerting antigen or tumor associated characteristic common to many pancreatic cancers. Bever hopes the combined approach will synergistically remove the breaks from the immune system and bring in T cells that will be specifically targeted to pancreatic cancer cells.

Immune therapy offers one of the only promising treatments for the most advanced pancreatic cancers that cannot be controlled with surgery, chemotherapy or radiation therapy.

Rare Findings Could Help Many

Rusty Johnson would like to better understand rare immune cells involved in regulating the immune system’s response to cancer. These are cells that are so poorly understood that they have not been written about in most medical textbooks. Johnson believes a better understanding of these cells may lead to new, targeted treatments that could improve the effectiveness of existing immune therapies.

He was inspired by his earlier research of the IDO pathway, a mechanism tumors use to suppress the immune system and one that has been associated with poor outcomes in many types of cancer. IDO’s normal function is to help regulate the immune response and prevent immune cells from attacking normal cells, but cancer cells co-opt it to hide from the immune system. Clinical trials of drugs that block IDO appear to make other immune therapies work better.

Johnson believes there are many other cells and pathways that play a role to immune suppression. “Figuring out the mechanism behind how those cells work is critical to discovering new targets to stimulate antitumor immunity,” he says. Some, like IDO, may work through checkpoints to regulate the immune system, but others may have another primary mechanism of action. “What they do and how they do it is currently a black box,” says Johnson.

He is particularly interested in improving the activity of the pancreatic cancer vaccine developed and moved to the clinic by his mentors, Elizabeth Jaffee and Daniel Lacheru. Vaccines accelerate the immune response, bringing in many powerful cancer-killing T cells only to be held at bay by checkpoint inhibitors, like IDO, PD-1, CTLA-4, LAG3 and others, which put the brakes on the immune response. “I believe there are cells that can be both accelerators and brakes, depending upon their cellular environment. We need to harness that power and use it against cancer,” says Johnson. Targeting these cells with drugs in combination with other therapies would potentially improve anticancer immunity, he says.

He is confident that Kimmel Cancer Center immunology experts can decipher the complexity of the immune response. He argues that cancer isn’t as smart as it is often portrayed. It doesn’t intelligently select these regulatory processes to save itself; it just gets lucky, he says. It blinds the cancer cell to a person working at a computer. “Rather than intelligently typing words into a computer, the cancer cell just presses a bunch of buttons on the keyboard until it finds one that works, and it keeps pushing it until it doesn’t work anymore,” says Johnson. “Cancer hasn’t outsprinted us. If it had, it would kill every time. It doesn’t. We get cures because we are smarter than the cancer. We just need to know what to target.”

That’s precisely what he is hoping to accomplish in the Jaffee lab, which he sought out specifically for its pioneering role in advancing cancer immunology research and its translation to patients. “The Kimmel Cancer Center is tremendously unique,” says Johnson. “It is the worldwide epicenter of pancreatic cancer and cancer immunology translational research because of Liz and Dan.”

Johnson says he came from an institution that did not embrace collaboration or have the strong donor involvement so common at the Kimmel Cancer Center. He says the intense and unique collaboration between scientists and clinicians at the Kimmel Cancer Center’s Skip Viragh Center is remarkably efficient at studying immunotherapy treatments and getting them into clinical trials. “We are at a center where you can study what you think is going to help others and have donors generous enough to provide the funding,” says Johnson.

Combining for a Cure

Valerie Lee is investigating a new treatment approach that may make currently incurable pancreatic cancers curable.

Working with Jaffee, Lacheru, Lee has been a focus for Zheng, an investigator in Jaffee’s laboratory. Murphy has zeroed in on one of the changes identified by Zheng. Targeting it, he believes, could simultaneously light the cancer and knock out a side effect.

Zheng’s research revealed Sema3D as a neural highway of sorts, allowing cancer cells to hitchhike on nerve cells to travel away from the main tumor. This painful invasion of nerve cells is also deadly because it is a mechanism the cancer uses to spread—a mechanism, Murphy says, that is currently untargeted in pancreatic cancer therapy.

He hopes to change that and is working with Jaffee and Zheng to develop therapies that could block Sema3D. “If we develop drugs that inhibit this process, we develop drugs that inhibit this process, we might be able to hijack the functions of cells around the tumor to create a cancer-friendly environment,” says Murphy.

No Pain, Significant Gain

Cancer patients have a knack for hijacking the functions of cells around the tumor to create a cancer-friendly environment. Blocking these changes has been a focus for Zheng, an investigator in Jaffee’s laboratory. Murphy has zeroed in on one of the changes identified by Zheng. Targeting it, he believes, could simultaneously light the cancer and knock out a side effect.

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Zheng and Ella-Mae Shupe. Lee’s focus is on locally advanced pancreatic cancer. Although the cancer has not invaded other organs (metastatic), it has begun to attach itself to the tissue and vessels around the pancreas and, as a result, it cannot be treated with surgery. About 40 percent of patients diagnosed have this form of the cancer. “Right now, we don’t have many treatment options for them,” says Lee. They receive the same treatment that patients with metastatic pancreatic cancer get, she says.

Lee’s approach could make curative surgery an option for many more patients. It combines anticancer drugs, a pancreatic cancer vaccine, an exciting new type of immune therapy known as an immune checkpoint blockade and a very precise form of radiation therapy called stereotactic body radiation therapy.

The therapy uses standard anticancer drugs to stabilize the cancer, followed by the Jaffee-developed pancreatic cancer vaccine. The vaccine awakens the immune system, summoning cancer-fighting killer T cells to the tumor. Treatment with a new checkpoint blockade immune therapy known as anti-PD-1 disrupts a mechanism cancer cells use to hide from these T cells. Lee hopes that together, these therapies will cause the patient’s own immune system to attack the cancer. Patients receive two doses of this combined regimen three weeks apart. Next, patients begin five days of radiation therapy. This treatment destroys pancreatic cancer cells and also awakens the immune system, Lee says. As cancer cells die, they release their proteins into the body. Essentially, they show their true colors to the immune system, which now recognizes them as abnormal cells; immunotherapy is then deployed to the tumor. Patients will then, hopefully, get surgery and chemotherapy, followed by more immunotherapy, with the goal of keeping the tumors at bay.

With funding support from the United Company Charitable Foundation and the James W. and Frances Gibson McGlochin Foundation of Bristol, Va, the Kimmel Cancer Center will soon begin a clinical trial in 54 patients to study the combined therapy. Lee wants to see if it works well enough against the cancer to get more patients to surgery, where their cancers could be cured. At a minimum, she hopes it will keep patients’ cancers from spreading—and potentially keep them in check for a long time.

Lee completed her fellowship in June 2016 and is helping expand pancreatic cancer clinical trials to the national capital region at Johns Hopkins’ Sibley Memorial Hospital in Washington, D.C.
May T un Saung is forming collaborations with Justin Hanes, Director of the Center for Nanomedicine, and Hai-Qiao Yan, Associate Director of the Institute for NanoBioTechnology, to develop nanoparticles that enhance tumor immunity. Nanoparticles are tiny nano-scale structures that are larger than molecules. In cancer medicine, they can be used to improve the effectiveness and efficiency of transporting drugs to tumors. Saung envisions nanoparticles loaded with tumor antigens to stir an immune response specifically against the cancer and immune therapy molecules on the surfaces to keep the immune response active.

Precision medicine approaches are possible as patients’ tumors could be sequenced to identify the specific molecules that may provoke improved immune signals against the cancer cells. Nanoparticles could include these molecules to generate an anti-tumor response specific to a patient’s, unleashing a more potent immune response against the cancer.

Liz Thompson is a new faculty member, collaborating with Mouth Cancer Center co-directors Elizabeth Jaffee and Daniel Lauber, clinician-scientist Lei Zheng and pathologist Alan Kornblatt. SHE is a surgical pathologist, she is focused on deciphering and characterizing the immune response at all stages of pancreatic cancer, particularly how immune activity changes in response to different types of immune therapies. She expects this research to reveal new immune targets for therapy and biomarkers that predict whether a cancer will or will not respond to immune therapy.

Thompson will compare tumors from patients whose biopsies obtained before treatment to samples taken at surgery. For pancreatic cancers that cannot be treated with surgery, she will use biopsies taken at different time points throughout diagnosis and treatment. Thompson will use advanced technologies, such as flow cytometry and DNA sequencing, to sort through and collect immune cells for study and to identify potential biomarkers that influence immune activity. In addition, a sophisticated technology known as multiplex immunohistochemistry will be used to visualize the spatial composition of immune cells within tumors.

"Cancers tend to change, mutating their DNA to survive in the face of different treatments," says Thompson. "This work will help us better understand and target these changes to keep the immune system active as the tumor evolves."

Her ultimate goal is to convert even the most advanced pancreatic cancers to a chronic, manageable disease.

Combinations That Make Vaccine Therapy Work Better

Mark Yarchoan, the Linda Rubin Fellow, is hoping to build upon Jaffee’s work on the pancreatic cancer vaccine. He is studying whether combining additional immunotherapies with the vaccine makes the killer T cells that make up the vaccine recruit to tumors better at destroying cancer cells. He and his team are focusing on combining the pancreatic cancer vaccine, cancer-fighting immune cells were not usually found in pancreatic tumors, says Yarchoan. "I'm hoping we can push immune therapy even further by adding in additional immunotherapies that make the T-cell tumor microenvironment more immunogenic."

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In the News

Molecular Conspiracy
A new genetic clue provides insight about how pancreatic cancer spreads. Three proteins, annexin A2, Sema3D and another molecule, conspire to create the lethal characteristics that define pancreatic cancer. Annexin A2 had previously been linked to poor survival rates, and this new finding by pancreatic cancer expert Lei Zheng reveals more information about how it works with the other two proteins to promote the spread of pancreatic cancer.

Zheng is collaborating with pancreatic cancer expert Elizabeth Jaffee on therapies that interfere with the proteins. "We are planning clinical trials with a recently developed vaccine to target annexin A2," says Zheng. "At the same time, we are developing a therapeutic antibody targeting annexin A2, and we are looking for another to target Sema3D."

The researchers are still working to decipher the molecular mechanisms at play but believe annexin A2 may work as a bodyguard of sorts for Sema3D, sheltering and guiding the protein as it makes its way toward an exit at the cell surface. It could also act like a professional packer, helping enclose Sema3D in tiny molecular bubbles that are secreted by cells, says Zheng. Once out of the cell, Sema3D works as a neural highway, allowing cancer cells to hitchhike on nerve cells to travel away from the main tumor. The findings align with other pancreatic cancer observations by Zheng and team. "Pancreatic cancers are what we call neurotropic, meaning they tend to invade nerves," says Zheng. Earlier pancreatic cancer vaccine research by Zheng found that long-term survivors who had been treated with the vaccine had antibodies against annexin A2 in their tumors. The research was funded by the National Cancer Institute (R01 CA169702, K23 CA148964-01, H1.42093; MOD FY15-226, P50 CA062924, P30 CA06973), the Viragh Foundation, the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, the Lefkofsky Family Foundation, and the Lustgarten Foundation.

Genetic Risks
In the largest study of its kind, researchers have connected alterations in five regions of the genome that increase the risk of developing pancreatic cancer. Individual changes in these regions increase pancreatic cancer risk from 12 percent to as much as 58 percent.

"The variations are common in the population, and most individuals who have them will never develop pancreatic cancer," says Alison Klein, a Johns Hopkins Bloomberg School of Public Health professor of oncology and principal investigator of a large international collaboration. "We knew there were genetic variants to be found, and the large number of pancreatic cancers in our analysis gave our study the power to find more novel genes," says Klein.

The team hopes to further increase the number of cancers studied to obtain even greater insight into the genetic variants associated with pancreatic cancer, one of the most lethal types of cancer. "We know from our analysis that there are lots of other variants we need to find to fully understand pancreatic cancer," says Klein.

The study also confirmed connections between pancreatic cancer risk and several genetic variants linked to other cancers. "The research was supported by the National Institutes of Health (RO1 CA154823)."

In 2015, when Swim Across America first began supporting the clinical trial, Forbes called it “the most exciting finding announced” when it was featured at the annual meeting of the American Society of Clinical Oncology.

Gift Supports New Drug Combo Approach
Anne Wyman, the Frederick W. Richmond Foundation, her daughter Elizabeth McCance and the McCance Foundation Trust made a generous donation to help Dung Le continue a study of a combined five-drug approach for pancreatic cancer called GTX-CL. It uses the drugs gemcitabine, docetaxel, capetitabine, cisplatin and irinotecan. This current study builds on a prior successful study with GTX-C initiated with funds from several donors, including Swim Across America and the Solomon Goldman Pancreatic Cancer Research Center. Le is studying lower, less toxic doses of the drugs as a way to attack pancreatic cancer at different points but also reduce treatment side effects.
New Skip Viragh Outpatient Cancer Building

Construction is well underway on the new $100 million, 184,000-square-foot outpatient cancer diagnostic and treatment facility slated to open in late 2017.

The building, which is named for Albert P. “Skip” Viragh, a Maryland mutual fund investment leader, philanthropist and Kimmel Cancer Center pancreatic cancer patient who died in 2003 of the cancer, will include a floor dedicated to promising new immune therapies for pancreatic and other gastrointestinal cancers. Funding for the building comes entirely from private philanthropy, including a $65 million gift honoring Viragh.

It will accommodate more than 180 daily patient visits and 60 to 80 new patient appointments each week. It will also be home to the multidisciplinary cancer clinics. The novel clinics are modeled after one established by the Skip Viragh Center for Pancreatic Cancer Clinical Research and Patient Care. The clinics offer newly diagnosed cancer patients a comprehensive consultation involving all of the specialists contributing to the treatment and diagnosis of their cancer type. By the end of the coordinated one- or two-day visit, patients receive a detailed treatment plan recommendation. “The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care and the Viragh Scholars program—established through the profound generosity of Skip Viragh—have made the Kimmel Cancer Center a powerhouse in developing new treatments for pancreatic cancer,” says Daniel Laheru, who cared for Viragh and now serves as co-director of the Skip Viragh Center. “The Viragh family has remained singularly focused on cancer care, helping countless numbers of patients. Skip is the heart of this new building.”

When completed, the new building will free up space in the Kimmel Cancer Center’s Harry and Jeanette Weinberg Building to expand inpatient cancer services, 24-hour urgent care, and blood and bone marrow cancer outpatient services.

“I can’t help but think what the future of cancer care will be like,” says Kimmel Cancer Center Director William Nelson. “In this place, I believe we will see the beginning of the end of cancer.”

Construction Milestone
A “topping out” ceremony, marking the placement of the final support structure atop the building, was held on Oct. 14, 2016.
Help Us Make a Difference

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

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

You may designate a gift to a specific faculty member.

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