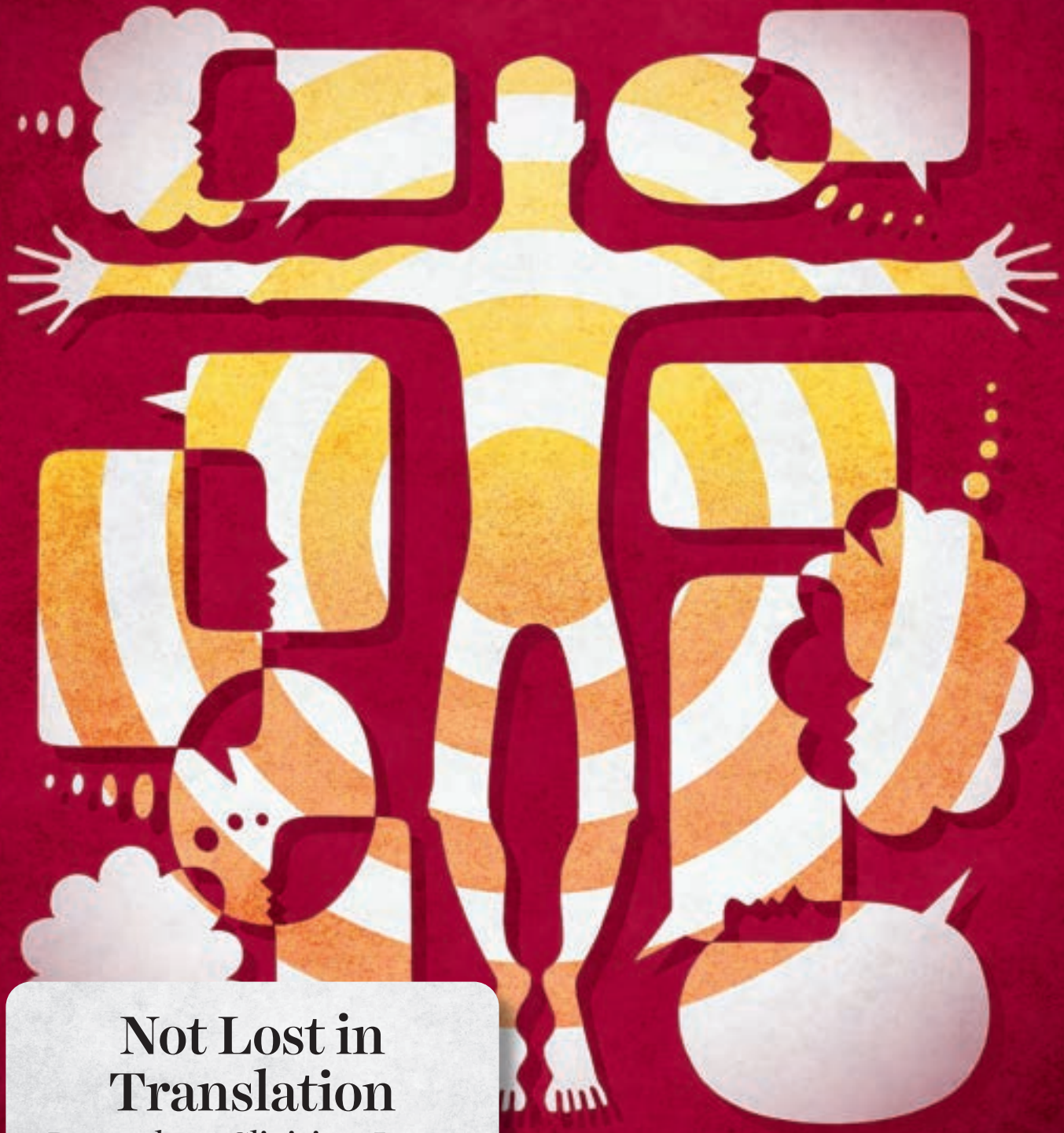
FOX CHASE

Forward

BROADENING THE CONVERSATION ABOUT CANCER | SUMMER/FALL 2022



Not Lost in Translation

Researchers, Clinicians Learn to Speak Each Other's Language

FOX CHASE CANCER CENTER
TEMPLE HEALTH


Jonathan Chernoff Robert Uzzo

AN ONGOING DIALOGUE

Collaboration is at the heart of translational research. It's about scientists and clinicians communicating regularly, each sharing observations from the lab or the clinic. Their insights form the basis of strategies and studies, pursued together, with one major goal: to translate research findings into real-life clinical outcomes that benefit patients.

We often hear the phrase "from bench to bedside," referencing both the basic science and clinical aspects of translational research. By sharing our work in each of these areas, we create an ongoing dialogue, a conversation that goes back and forth, in both directions, bringing us closer to uncovering the latest breakthroughs in cancer care.

In this issue of *Forward*, we delve into the translational work of our Fox Chase Cancer Center and Temple Health faculty. The ideas they raise, the questions they ask and seek to answer, the problems they are working to solve. These things are all very exciting and they are happening right here.

Translational research is paving the way for the development of novel personalized medicine approaches that tailor treatment to an individual's specific cancer. It is helping us make advances in areas of emerging interest and growth such an immunotherapy—a type of treatment that jumpstarts the body's immune system to fight cancer.

This work informs how we are treating patients with a variety of different cancers, from melanoma to lymphoma to ovarian cancer, pancreatic cancer, bladder cancer, and prostate cancer. We are also focusing on rare cancers, such as gastrointestinal stromal tumors, as well as specific populations, such as "never smokers" with lung cancer.

We are examining previously unexplored avenues of cancer development, identifying new targets for drug development, and even addressing barriers to care within our community such as access to screening and lack of follow-up care.

Cancer is complex. No one working on their own can answer the many questions of how and why and what works best. It takes a team. This is why translational research is so powerful. It brings together professionals from multiple disciplines. Each individual has their own expertise and experience and offers their unique contributions to the process.

The connections we have with each other as investigators help us expand our thinking and accelerate the pace of research. Our patients provide the inspiration and so often are our partners in carrying this research forward.

We consider it a privilege to steward this important work and we will continue to forge on.

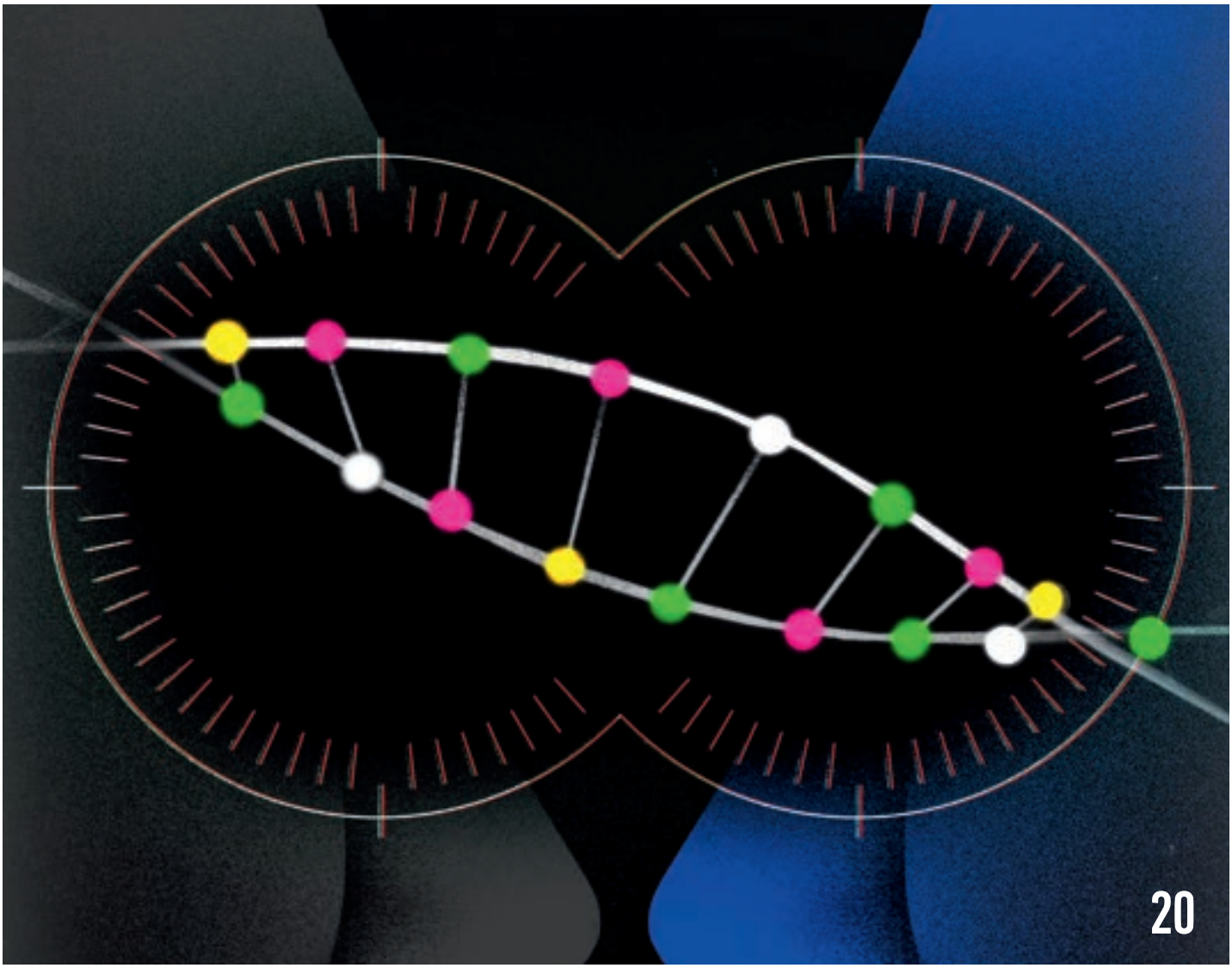
With you. And for you.

Jonathan Chernoff, MD, PhD
CANCER CENTER DIRECTOR

Robert Uzzo, MD, MBA, FACS
PRESIDENT AND CEO

COLIN LENTON

FOX CHASE
Forward
SUMMER/FALL 2022



BRIAN STAUFFER

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FORWARD magazine is published twice a year for friends of Fox Chase Cancer Center by the communications department of Fox Chase. One of the leading cancer research and treatment centers in the United States, Fox Chase was founded in 1904 as one of the nation's first cancer hospitals, and was among the first institutions to be designated a National Cancer Institute Comprehensive Cancer Center in 1974. Fox Chase joined Temple University Health System in 2012.

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CARDONI

STUDYING MUTATIONS IN COLORECTAL CANCER PATIENTS TO ENHANCE CLINICAL TARGETING

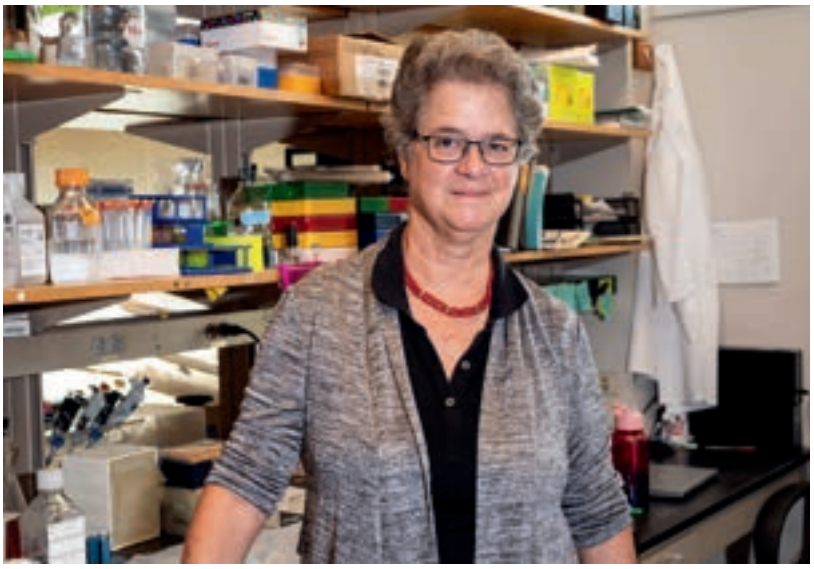
In a new study in the prestigious journal *Nature Communications*, researchers at Fox Chase Cancer Center identified distinct patterns of mutation in specific subsets of colorectal cancer. The finding could help clinicians administer available therapies to colorectal cancer patients in a more personalized way.

"This study was investigating a gene called PTEN, which is a tumor suppressor. In colorectal cancers, PTEN is mutated in 8% to 10% of tumors," said Erica Golemis, Deputy Chief Science Officer at Fox Chase.

"Specific types of mutations in genes can have varying effects on the proteins they encode. For PTEN, mutations can have little effect or can have a large effect on the protein's enzymatic activity, the protein's abundance, or both. What kind of mutation a tumor has affects how it responds to treatment."

> "The fact PI3K is an important drug target suggests some important follow-up studies."
>
> —**ERICA GOLEMIS**, DEPUTY CHIEF SCIENCE OFFICER

Golemis worked on the study with Joshua E. Meyer, vice-chair for translational research in radiation oncology, who is interested in defining patterns of mutation characterizing colon versus rectal cancers and in old versus young patients to aid his treatment of these cancers. Meyer noted that there are clearly defined subsets of colorectal cancer with different abundance in the population and distinct prognosis.



Erica Golemis (top) and Joshua E. Meyer (left) are working on ways to help colorectal cancer patients receive more personalized therapies.

THOMAS C. STEPHANO

In the less common subsets, it has previously been impossible to identify specific patterns in genes such as PTEN, because the number of analyzed tumors was too small. To address this, a team led by Ilya Serebriiskii, a research associate professor in the Golemis lab, used a large cohort from a genomics company, Foundation Medicine, to examine and identify several patterns of PTEN mutation in distinct subsets of PTEN and in tumors found in the colon versus the rectum.

"We found patterns of co-occurrence, where mutations in PTEN tended to be found together with mutations increasing activity of a second protein, PI3K, but only in some subsets of colorectal cancer," said Golemis. "The fact that both proteins tend to be mutated together suggests a need for some tumors to strongly activate this pathway and that reduced PTEN function is not enough to do it alone. The fact PI3K is an important drug target suggests some important follow-up studies."

REKINDLING IMMUNOTHERAPY RESPONSIVENESS BY MIMICKING THE FLU IN TUMORS

In a study published in the prestigious journal *Nature*, Fox Chase Cancer Center researchers have shown that a drug candidate may help re-initiate immune responses by mimicking influenza virus infections in patients whose cancer is unresponsive to immunotherapy.

Immunotherapy, which harnesses the power of the body's immune system to attack cancer cells, has great potential for patients who do not respond to other treatments. But the number of patients who are successfully treated with immunotherapy is small because many tumors are immunologically silent, or "cold," meaning they have adapted characteristics which trick the immune system into ignoring them as a threat.

Siddharth Balachandran, co-leader of the Blood Cell Development and Function research program, and his colleagues were able to identify a particular compound called CBL0137 that can trigger necroptosis, a highly inflammatory form of cell death within tumors, and turn these "cold" tumors "hot."

"We know that influenza viruses trigger very potent immune responses in infected cells. We thought, 'What if we could find a way to mimic a virus infection within a tumor that was otherwise cold?' That way, the body's own immune system could fight the tumor as if it were virally infected tissue," said Balachandran.

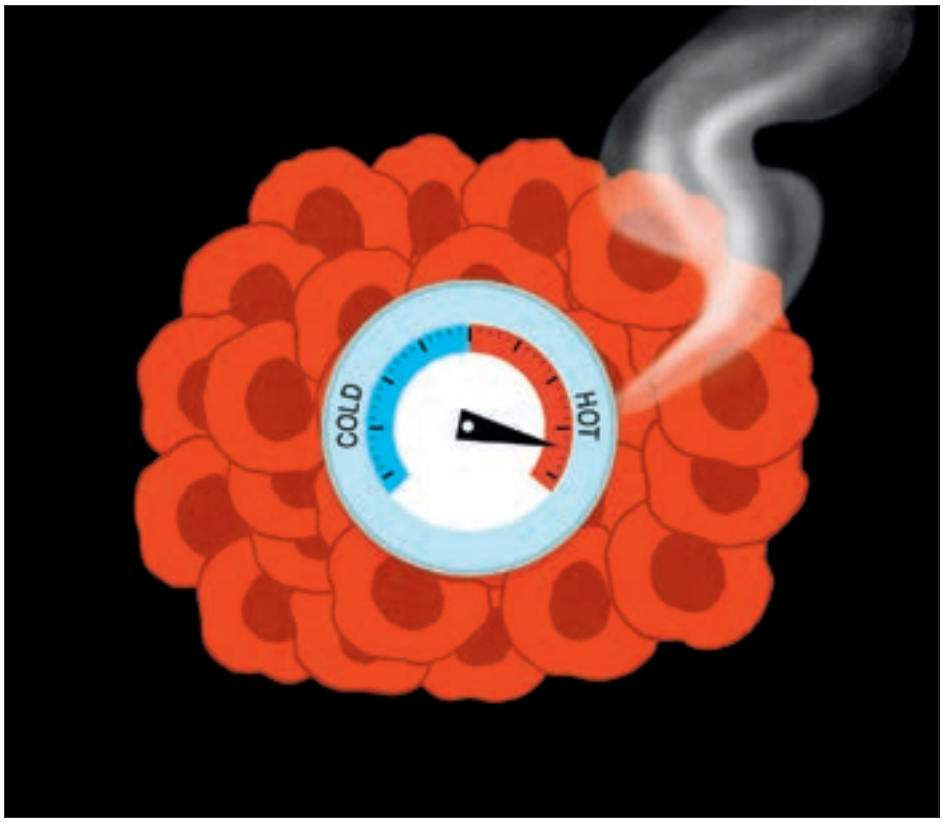
The researchers found that by administering CBL0137 directly into tumors in mice, an antiviral response is induced within the tumor mass and the immune system is alerted to its presence.

"This is an important study for patients who have failed first-line immunotherapy."

—**SIDDHARTH BALACHANDRAN**, BLOOD CELL DEVELOPMENT AND FUNCTION RESEARCH PROGRAM

"This is an important study for patients who have failed first-line immunotherapy, because combining a 'virus mimetic' immune adjuvant with immunotherapy offers the opportunity to rekindle an immune response and make immunotherapy effective in otherwise unresponsive patients."

Balachandran added that the compound is already in clinical trials as a standard chemotherapeutic, so researchers know it's safe. Clinicians at Fox Chase will be conducting a phase 1 clinical trial later this year in which the compound will be used alongside immunotherapy drugs for testing in immune-relapsed melanoma.



JAMES STEINBERG

FOX CHASE RECEIVES PRESTIGIOUS GRANT TO EXPAND UNDERGRADUATE RESEARCH OPPORTUNITIES

Fox Chase was awarded an $822,000 Research Education Program grant that will allow the center to expand the reach of its University of Delaware-Fox Chase Cancer Center Summer Research Fellowship.

"The goal of this program is really to allow students who may not even consider a career in STEM the opportunity to see what it's like to have a hands-on experience in a lab and possibly change their career trajectory," said Amanda Purdy, director of Academic Affairs at Fox Chase.

"With the funds from this grant, we will be able to expand this existing pilot program from serving four students per summer to 12."

The goals of the program, which will be funded by the National Cancer Institute, will include fostering a better understanding of biomedical, behavioral, and clinical research and its implications, as well as enhancing the training of a workforce to meet the nation's biomedical, behavioral, and clinical research needs.

"With the funds from this grant, we will be able to expand this existing pilot program from serving four students per summer to 12."

—**AMANDA PURDY**, DIRECTOR OF ACADEMIC AFFAIRS

RICHARD MIA

The fellowship is a partnership between the University of Delaware and Fox Chase. The idea was hatched during a discussion over coffee by Glenn Rall, chief academic officer at Fox Chase, and Thomas W. Hofmann, a member of the Fox Chase Board of Directors, a graduate of the University of Delaware, and a member of the university's President's Leadership Council.

The pilot program aimed to serve as a way to bring talented students from the University of Delaware to Fox Chase for enhanced summer internships that would provide them not only research training, but also mentoring on creating and giving presentations, reading scientific literature, and developing useful professional networks.

Through the summer research fellowship, the students are provided with paid, full-time, and immersive summer research opportunities. During the 10-week residential program, research fellows work on unique projects and hone their laboratory skills. At the culmination of the program, students present the results of their research at a symposium.

Not Lost in Translation

Researchers, Clinicians Learn to Speak Each Other's Language

Translational research, which has become more prominent over the last few decades, takes findings from basic science done in the lab and applies them to the treatment of patients. However, the process can also go in the other direction, with observations at the bedsides of patients being taken into the lab.

But whether starting in the lab or at the bedside, translational research is key to advancing the fight against cancer, and at Fox Chase Cancer Center, the research is interdisciplinary, involving researchers and physicians from various specialties. By learning to speak each other's language, they can better understand how cancer emerges, how to detect it, and how to better treat it.

Although translational research is often associated with the development of new drugs, it includes many other points of focus, including diagnostics and community impact, areas that directly affect patients, making it paramount that clinicians and researchers are well-versed in what the other is developing. The impact of this partnership can be seen in the use of clinical

BY MARIAN AURIEMMA

ILLUSTRATIONS BY DAREN LIN

trials investigating new therapies or targets and in community research that leads to more effective outreach.

Fox Chase has historically focused on such bench-to-bedside approaches to find tangible solutions to some of medicine's biggest roadblocks. This special section focuses on the work currently being done by Fox Chase and Temple Health faculty, spanning multiple fields with the ultimate goal of translating results to real-life clinical outcomes.

Clinical Trials Changing Melanoma

Investigator-initiated trials to bring new therapies and treatments into the clinic have always played an important role at Fox Chase. With these trials, scientists can investigate new therapies and address challenges patients face throughout their cancer journey. Patients are able to reap the benefits of collaboration between clinicians and basic scientists.

For example, immunotherapy, which harnesses the power of the body's immune system to attack cancer, is considered the next frontier in cancer treatment because some patients who are unresponsive to chemotherapy and radiation and have no other options respond to it. But that number is small, and even those patients do not see lasting remission. The reason most tumors do not respond to immunotherapy is because the immune system does not see them as a threat. These tumors are referred to as "cold tumors."

"We know that influenza viruses trigger very potent immune responses in infected cells. The entire immune system rushes to the site of infection and quickly eradicates the infected cells," said Siddharth Balachandran, co-leader of the Blood Cell Development and Function research program. "We thought, 'What if we could find a way to mimic a virus infection within a tumor that was otherwise cold?'"

Balachandran conducted such research with an international team of scientists and it was published recently in the prestigious journal *Nature*. Anthony Olszanski, vice chair of Clinical Research for the Department of Hematology/Oncology, is now taking this research into the clinic. "The trial that we're currently working on involves immunotherapy and the use of the drug curaxin," said Olszanski. "We're hoping to run this trial in a very unique population, patients with melanoma that can be removed with surgery."

Curaxin is an anticancer drug that has been shown to reverse unresponsiveness in immune-checkpoint blockades. The trial that Olszanski is conducting is based on research

conducted by Balachandran and colleagues. They were able to identify a particular compound called CBL0137—which is in a family of curaxins—that could trigger necroptosis, a specific kind of cell death, by acting like a virus.

"This is also an important concept for patients who have failed first-line immunotherapy, because combining a 'virus mimetic' immune adjuvant with immunotherapy offers the opportunity to rekindle an immune response and make immunotherapy effective in otherwise unresponsive patients," Balachandran said.

New Targets in Sarcoma

Translational research is particularly important in rare cancers such as gastrointestinal stromal tumors (GIST). As scientists continue to uncover new targets and drugs for treating this cancer, obstacles such as drug resistance and side effects continue to be challenges, making collaboration between the clinic and laboratory pivotal.

Lori Rink, a researcher in the Molecular Therapeutics research program, has been working with Margaret von Mehren, chief of the Division of Sarcoma Medical Oncology, in identifying a potential new target, a serine/threonine kinase known as Wee1, for the treatment of GIST. Kinases are proteins that control important functions in the cell and can cause tumor cells to grow uncontrollably, leading to tumor formation.

"I'm really lucky to be working with Dr. von Mehren at a place like Fox Chase where we have access to a lot of rare patient specimens," said Rink. "For translational science, those are the best specimens to interrogate for novel targets because they are the most clinically relevant."

Such specimens are more important than ever for patients dealing with GIST, as current treatments for rarer subtypes such as PDGFRA D842V-mutant disease are often associated with difficult side effects. Patients with this subtype do not respond to imatinib, a kinase inhibitor used for the treatment of GIST for over 20 years. Although newer treatments like avapritinib are effective first-line therapies for patients with this subtype, cognitive side effects and drug resistance are issues, Rink said.

In one of her recent studies, Rink showed that when used in combination with avapritinib in KIT- and PDGFRA-mutant GIST cell lines, the Wee1 inhibitor adavosertib has a synergistic effect. In addition, the study showed that adavosertib was also effective when used alone in an engineered PDGFRA-mutant cell line. In ongoing research, they are combining adavosertib with lower doses of avapritinib in an effort to demonstrate the same cancer-fighting effectiveness while avoiding cognitive side effects and drug resistance.

In addition to testing this combination in various cell-line models, Rink said they are also testing it in patient-derived xenograft models, which are particularly important for translational purposes because tumor tissue is tested by being taken directly from a patient and implanted into mice.

"The cell lines that we use that have been derived from tumors, or the patient-derived xenograft mouse models that are growing the human tumors, are important resources for the lab because they allow us to perform mechanistic studies to understand how the targets are important in GIST and to test the efficacy of inhibiting these targets," Rink said.

She added that what makes her team's work so unique in the realm of translational medicine is that it does not take the typical path from bench to bedside. Instead, Rink described her team's work as starting at the bedside, moving to the bench, and then hopefully, making it back to the bedside.

"That's the beauty of Fox Chase," she said. "Not only is there collaboration among the basic scientists, but also with the clinical faculty. We teach each other a lot and ask each other a lot of questions, which is really important in this process."

"That's the beauty of Fox Chase. Not only is there collaboration among the basic scientists, but also with the clinical faculty. We teach each other a lot and ask each other a lot of questions, which is really important in this process."

—**LORI RINK**, MOLECULAR THERAPEUTICS RESEARCH PROGRAM

Estrogen and Lung Cancer

Translating findings into tangible therapies for patients requires an in-depth understanding of how specific types of cancers develop. That's the aim of the work being done by Joseph Treat, medical oncologist and medical director of Ambulatory Care, and J. Nicholas Bodor, thoracic oncologist and co-founder of the Never Smokers Lung Cancer Clinic.

"We are seeing more and more patients in our clinics diagnosed with lung cancer who have no smoking history. And the scary thing is, we don't exactly know what causes

it," said Bodor. "Never smokers with non-small cell lung cancer are a unique population," added Treat. "They typically are women who have different molecular profiles from that of smokers—50% have EGFR driver mutations. This has major therapeutic implications for the effectiveness of immunotherapy."

That's one reason Treat, Bodor, and the lab of Margie Clapper, Deputy Scientific Director and co-leader of the Cancer Prevention and Control research program, have focused on the role hormones may play in the disease. Clapper has investigated the mechanism by which metabolites of estrogen may promote non-small cell lung cancer in never smokers, as well as the basis for elevated levels of specific catechol metabolites in some patients.

Other researchers have studied the role of estrogen in lung cancer, but the Fox Chase team is the first to discover that the lung can metabolize estrogen to derivatives like 4-OHEs, which are known to be probable carcinogens. Previous studies by Clapper found higher levels of 4-OHEs in lung tumors.

"We have also recently found that levels of 4-OHE are higher in the urine of patients with EGFR-mutated lung cancer as compared to cancer-free individuals," Bodor said. He notes that these findings are still preliminary, but recruitment is ongoing from the Fox Chase clinics to increase the number of participants in this study.

"Everything we do here at Fox Chase is focused on developing better treatments or preventing this disease. While these data are exciting, we can't celebrate until we can actually make a difference in the lives of our patients," said Bodor.

"Everything we do here at Fox Chase is focused on developing better treatments or preventing this disease. While these data are exciting, we can't celebrate until we can actually make a difference in the lives of our patients."

—J. NICHOLAS BODOR, NEVER SMOKERS LUNG CANCER CLINIC

Cellular Therapies and Personalized Medicine

Cellular therapy research at Fox Chase and Temple Health have helped translate new findings in the lab into therapies that can overcome some of medicine's biggest challenges. These new approaches can be particularly useful for patients diagnosed with cancers such as Hodgkin lymphoma, an immune system cancer that begins in white blood cells. Yibin Yang, a scientist in the Blood Cell Development and Function research program at Fox Chase, recently co-authored a study that may help identify new ways to treat patients whose cancer is resistant to standard treatment.

Currently, brentuximab vedotin (BV) is one of the most effective therapies for patients with relapsed Hodgkin lymphoma, but many patients do not experience complete remission and develop resistance to BV. In Yang's study, researchers found that certain enzymes can help the body to respond again to the use of BV for the treatment of Hodgkin lymphoma.

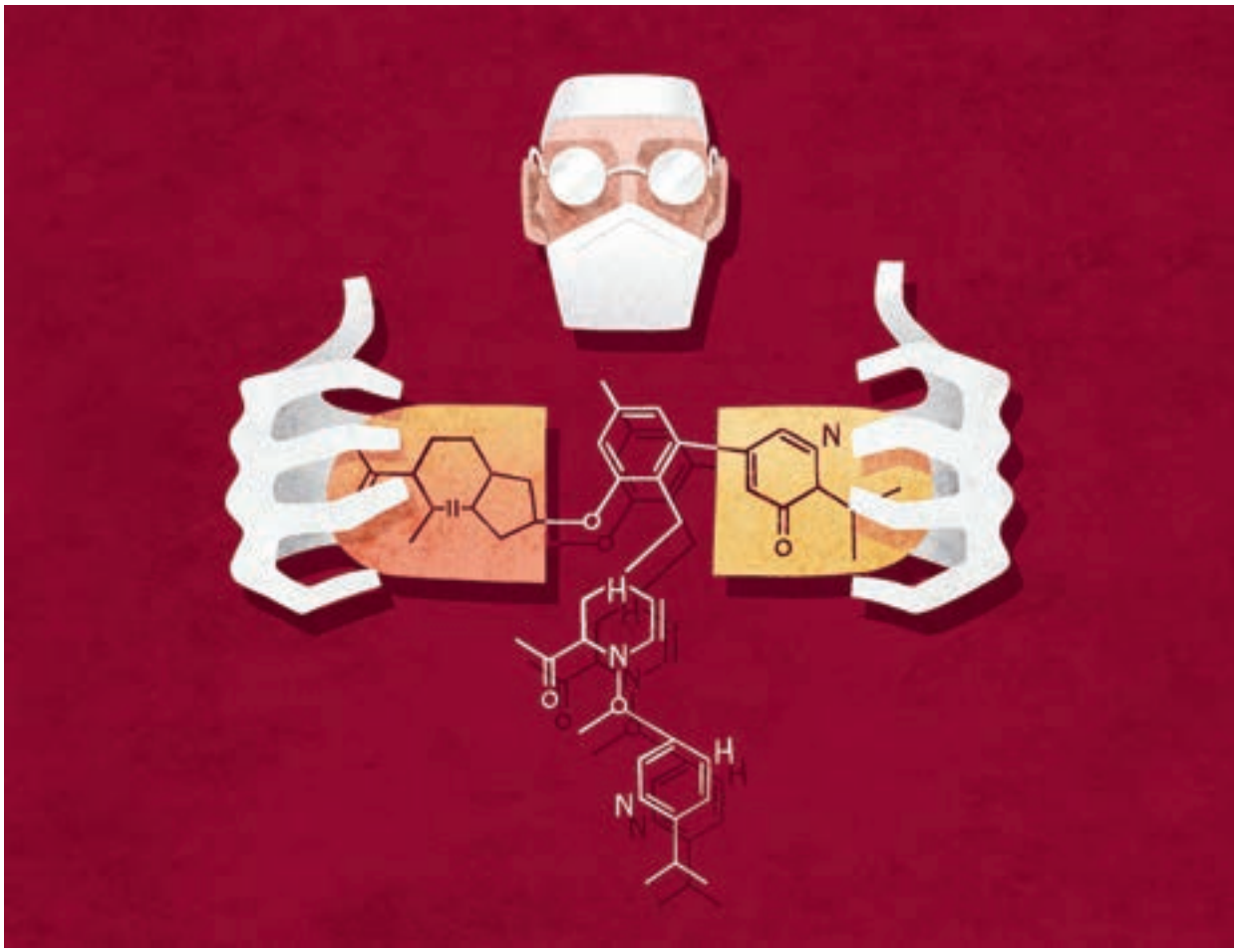
Researchers identified these enzymes through the CRISPR library screening platform, a laboratory tool used to change pieces of a cell's DNA. Yang and his team used this platform to carry out a screen against BV to identify genes that regulate how the drug responds in the bodies of patients being treated for Hodgkin lymphoma.

"Our identification of this previously unrecognized mechanism provides novel knowledge of possible BV responsiveness and resistance mechanisms in Hodgkin lymphoma, as well as leads to promising hypotheses for the development of therapeutic strategies to overcome BV resistance in this disease," Yang wrote in the study, which was published in *Clinical Cancer Research*.

A Temple investigator is exploring another type of cellular therapy. Tomasz Skorski, director of the Fels Cancer Institute for Personalized Medicine and associate director at Fox Chase, recently published a paper identifying a new drug combination that may assist in making myeloproliferative neoplasms more susceptible to cell death. These neoplasms are a kind of malignant blood disease that begins with stem cell mutations that cause an overproduction of cells. The growth of the neoplasms is fueled by oncogenic tyrosine kinases, which modulate many cell functions, including cell signaling, growth, and division.

Numerous neoplasms express these oncogenic tyrosine kinases that cause them to accumulate high numbers of toxic DNA double-strand breaks, but the cells are able to repair these breaks. With this in mind, Skorski and colleagues hypothesized that myeloproliferative neoplasm cell survival may depend on double-strand break repair mechanisms.

"There are some FDA-approved oncogenic tyrosine kinase inhibitors that slow these neoplasms down, but the drugs don't cure them," said Skorski. "When these neoplasms are



treated with these drugs, the cells very quickly lose the ability to repair the breaks in the DNA and become very vulnerable to the inhibitors of the DNA repair pathways."

To explore this issue, researchers examined the use of the oncogenic tyrosine kinase inhibitor ruxolitinib and the PARP inhibitor olaparib, a type of targeted therapy used to keep cancer cells from repairing their damaged DNA. These drugs were tested with and without the use of the chemotherapy drug hydroxyurea in preventing DNA damage repair and inducing cell death in neoplasms.

The study showed that this combination of ruxolitinib and olaparib, plus or minus hydroxyurea, ultimately led to an irreparable accumulation of lethal DNA breaks that resulted in the elimination of myeloproliferative neoplasm cells. "We are looking to do a clinical trial at Fox Chase on this research and apply it as a personalized medicine approach," said Skorski.

Identifying Disparities in Melanoma

Investigating previously unexplored avenues of cancer development has proven an important approach in cancer research. By taking a fresh look at a long-studied disease, researchers are able to probe unexplained aspects that can lead to changes in treatment.

Through a three-year research grant funded by the U.S. Department of Defense, researchers Nora Engel and Raza Zaidi, associate professors at the Fels Cancer Institute for Personalized Medicine at Temple and Fox Chase are doing just that as they work on identifying sex disparities in melanoma, specifically among military personnel, research that could ultimately affect treatment.

"Males are at higher risk for melanoma than females and suffer worse outcomes. What we found was that while military individuals are at higher risk for melanoma than the general population, males were at still higher risk than females," said Engel. "Our project seeks to determine the factors that lead to that higher risk." Engel said many studies have been done on the possible causes of melanoma disparities, including hormones, but nothing has been done to distinguish hormonal factors and the differences in sex chromosome composition.

"Every cell has either an XX or an XY composition depending on males or females, and these chromosomes have genes that are expressed that can regulate transcriptional patterns in a different way between males and females," said Engel. Effects on melanoma development may result from interactions between these sex chromosomes and hormones either working together or against

each other. "There might also be independent effects," she added.

Engel and colleagues used mouse models to produce both male and female XX-composed mice as well as XY-composed male and female mice. By comparing both male and female mice of the same chromosome composition, researchers were able to observe only the hormonal differences. Similarly, comparing an XX-composed male with an XY-composed male, for example, allows them to observe differences regulated by sex chromosomes.

The question of whether melanoma is regulated by

Taking the Clinic to the Community

Although most of the translational work at Fox Chase takes place in laboratory or clinical settings, some of it is conducted in the surrounding community. In order to affect change in cancer diagnosis and treatment, behavioral scientists like Carolyn Fang, associate director of Population Science, focus on make-or-break issues such as barriers to care.

For example, in the past, cervical cancer screening was primarily done in the clinic through the Pap test, a procedure in which a small brush is used to gently remove cells from the cervix to detect early signs of cervical cancer. "But we've found that when tests and advances are limited to the clinical setting, not everybody is able to take advantage of these new discoveries," said Fang. "Many women still face barriers to clinic-based screening."

To address this, Fang is working with Grace Ma, associate dean for Health Disparities and founding director of the Center for Asian Health at the Lewis Katz School of Medicine at Temple University, and Christina Chu, interim chief of the Division of Gynecologic Oncology at Fox Chase, to develop a way to make these tests more available to women who may face these barriers. One way they've explored this is by looking at the possibility of at-home cervical tests. "Large-scale studies have found that at-home tests are sensitive and reliable. The results from them are just as reliable as if a clinician obtained that sample in the clinic," said Fang.

Fang and her lab are also conducting an ongoing study of low cervical cancer screening rates for Asian-American women. "When you look at the aggregate data for Vietnamese, Korean, or Chinese women, you see significant differences across these ethnic groups," said Fang. "So we are working with community groups such as women's organizations, Korean churches, and Vietnamese community based organizations to reach Korean- and Vietnamese-American women specifically, because those two ethnic groups have traditionally had very low rates of cervical cancer screening."

In their study, Fang and colleagues provide these community members with information on clinical screens, information on at-home sampling, and a test kit. All women who participate are also encouraged to see their doctors for routine care.

Additional studies are being conducted by Suzanne Miller, a professor in the Cancer Prevention and Control research program, to explore the use of online and digital technologies designed to improve patient treatment decision making, self-management, and follow up on medical recommendations.

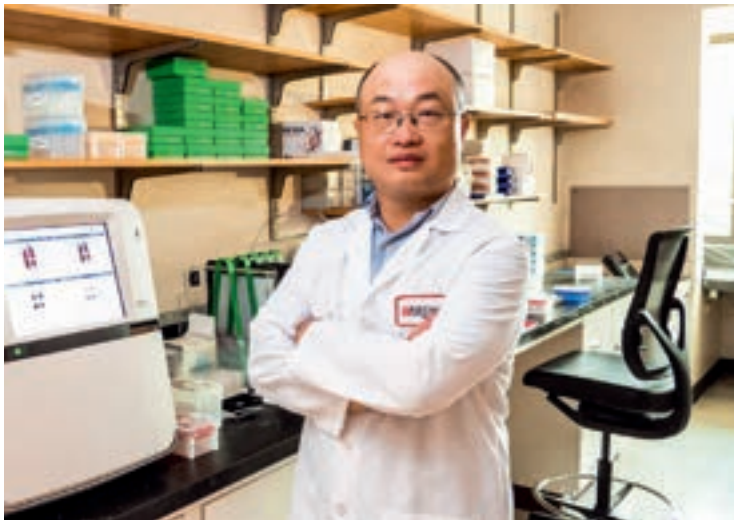
"We are very excited as behavioral scientists about the explosion of technology, drug discovery, and device production that is being generated by our basic science and clinical colleagues," said Miller. "However, at least as important as that is bridging the gap between the availability of these discoveries and bringing them to the patients and community members they are intended to serve."

Miller has been working with Enrique Hernandez, chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the Katz School of Medicine, to develop and evaluate the impact of evidence-based programs for underserved inner-city women. These programs are designed to provide communication interventions to reduce disparities in the incidence of cervical cancer, one of the few preventable cancers.

"In one set of studies, we contacted patients after an abnormal Pap smear to discuss barriers to making an appointment for a follow-up diagnostic procedure," Miller said. "We asked them what makes it difficult to come in—anxiety, educational barriers, or practical barriers like child care or transportation—and counseled to those barriers."

The telephone counseling program was very successful—rates of attendance for the first appointment went from under 50% to about 75%. "That was gratifying and exciting in terms of cancer prevention and control. However, unlike effective new medical advances that are readily delivered by physicians, the scope of the clinical system is not designed to incorporate these psychosocial innovations into clinical practice," Miller said.

"Our hope now is to change clinical practice so that these procedures and protocols can be built into healthcare delivery without increasing the burden on clinical staff and resources," she added.



Fox Chase and Temple Health faculty working on translational research, clockwise from top left: Gina Mantia-Smaldone, Division of Gynecologic Oncology at Fox Chase; Nora Engel, Fels Cancer Institute for Personalized Medicine at Temple; Yibin Yang, Blood Cell Development and Function research program at Fox Chase.

CLOCKWISE: DAVID DEBALKO, JOSEPH V. LABOLITO, THOMAS C. STEPHANO

sex chromosomes or hormones has been a dilemma for researchers for many years. "Cancer therapies are usually given regardless of the sex of the patient, so this would be another avenue of personalized medicine where the sex of the patient can also be a factor in what kinds of therapies will be given and how the patient will respond," said Zaidi.

Collaboration Fuels Advances in Ovarian Cancer

Determining different processes in cancer development is paramount when it comes to translating research into tangible treatments that can improve patient outcomes. James Duncan, associate professor in the Cancer Signaling and Epigenetics research program, has been working with gynecologic and surgical oncologist Gina Mantia-Smaldone to determine the roles of protein kinase activity in ovarian cancer.

"We collaborate with Dr. Mantia-Smaldone in collecting tumor samples from the clinic. We then use our proteomic technology to identify protein kinases that are highly expressed in these tumors so that we can explore them as new drug targets," said Duncan. Proteomic tools can help identify overall proteins present in a cell, tissue, or organism. In particular, Duncan said they are looking at a group of kinases called MRCK that are involved in metastases.

Uncontrolled protein kinase activity has been linked to the development of nearly 25% of all cancers; consequently, protein kinases represent one of the most promising avenues for cancer therapy. In a paper published in 2020, Duncan and Mantia-Smaldone identified new potential kinase drivers in ovarian cancer and have since been working on determining the role these kinases play in promoting ovarian cancer.

"We're also working to collect samples of metastatic ovarian cancer and trying to determine whether this kinase that we've identified has any kind of therapeutic response in terms of either causing the tumor cells to die or blocking their cell growth," said Duncan.

"These protein kinases represent really good targets for treatment," he added. "They've shown tremendous success in many other types of cancer, so we believe that targeting and understanding these kinases in ovarian and endometrial cancers will provide new therapeutic avenues to improve the survival of patients." ◆

Cross-Pollinating Pancreatic Cancer Research

Translational Medicine Makes Innovation Flower at Greenberg Pancreatic Cancer Institute

The Marvin and Concetta Greenberg Pancreatic Cancer Institute, which was founded at Fox Chase Cancer Center in 2017, is a leader in translational research and medicine, a collaborative approach in which scientists take findings from their laboratory benches into the clinic and physicians bring their clinical research findings into the lab. This interaction allows researchers and physicians to better understand how cancer emerges and how to detect and better treat it.

BY MARIAN AURIEMMA
ILLUSTRATIONS BY JASON HOLLEY

Fox Chase prides itself on leading the way in this type of cross-pollination, on its ability to conduct specialized research by harnessing the expertise of multiple disciplines. This work has led Fox Chase to become the only cancer center in the Philadelphia region to be designated as both a Clinical and Academic Center of Excellence for Pancreatic Cancer by the National Pancreas Foundation.

"What makes this cancer institute unique is the collaborative efforts amongst leaders in each of their own disciplines with one common goal, the integration of science and patient-directed care," said Sanjay Reddy, a surgical oncologist and one of the co-directors of the institute. "This approach is the foundation for success and is supported by not one discipline alone but the collective hive mentality of each member."

The institute epitomizes this type of research through its multifaceted approach to treating this understudied disease. It strives to move new discoveries from the lab to the clinic—from the bench to the bedside—through the three pillars of a comprehensive cancer center: basic biology, clinical medicine, and population science. At the institute, a multidisciplinary team of researchers and physicians work to develop innovative ideas to foster collaborative efforts and treat those with pancreatic cancer in the most innovative and comprehensive way possible.

"I'm lucky that I get to collaborate with some really outstanding clinicians in other departments and we can figure out how to dovetail our different treatments, whether it's radiation and chemotherapy, or surgery."

—JOSHUA MEYER, VICE CHAIR OF TRANSLATIONAL RESEARCH

The fruits of this unique cross-pollination approach to treatment can be seen in the clinical trials currently underway at the institute. These studies include investigating a new method for administering radiation therapy, testing novel drug combinations that could better fit geriatric patients, and investigating how pancreatic tumors get essential nutrients in the absence of blood supply, among others.

COLLABORATION CORNERSTONE

The institute's founding was funded by philanthropist Concetta Greenberg to honor her husband, Marvin, who passed away from pancreatic cancer. Since its establishment, the institute has played a pivotal role in developing treatment breakthroughs through seamless collaboration among researchers. In addition to Reddy, the institute has two other co-directors: Edna "Eti" Cukierman, a highly accomplished scientist who is also co-leader of the Cancer Signaling and Epigenetics research program, and Igor Astsaturov, a physician-scientist who is also an associate professor in the Department of Hematology/Oncology.

Reddy, one of the many clinicians who represent the institute, said his role is to bring his surgical expertise to the forefront when designing clinical trials in this space. Other leaders such as Efrat Dotan, division chief of the Gastrointestinal Cancer Program, and Joshua E. Meyer, vice chair of translational research in the Department of Radiation Oncology, play a pivotal role in developing these types of trials.

"Many of our clinical trials are designed under the premise of utilizing neoadjuvant therapy, which includes chemotherapy and/or radiation, before attempts at surgical removal of tumors are made," Reddy said.

"In the majority of those with pancreatic tumors, the location oftentimes dictates this treatment approach due to

involvement of nearby organs or blood vessels. Therefore, any advantage we can obtain to have these tumors recede, we embrace."

The collaborative efforts between physicians and scientist are at the core of what the institute is built upon. "We have learned that pancreatic cancer is a unique disease that involves multiple specialties spanning not only the clinical side of medicine, but equally important, the basic science side," Reddy said.

SCIENCE-BASED THERAPIES

Cukierman and Astsaturov both play essential parts in leading the institute toward novel, science-based therapeutic interventions. "On the bench side we're really trying to do work that is clinically relevant. On the other side, we're trying to ensure that the clinical trials and clinical

Physician-scientist and medical oncologist Igor Astsaturov (left) and surgical oncologist Sanjay Reddy (above) are two of the co-directors of the Greenberg Pancreatic Cancer Institute.

interventions we're to introduce are fully based on proven biology," said Cukierman.

"Because we're all together in the same room either discussing new ideas that can be taken to the bench or new ideas that can be taken to the clinic based on some advancements at the bench, we all put our heads together, so there's a synergy," she added.

Among many other collaborations, Cukierman and Astsaturov have begun in-depth analysis of the role cancer-associated fibroblasts (CAFs) play in pancreatic cancer. Their teams are investigating how CAFs provide tumor cells with essential lipids, such as cholesterol, that help them grow. They are also developing new strategies to disrupt CAF-cancer cell interactions, a project being led by senior postdoctoral fellow Charline Ogier.

Additionally, the institute's teams are working with researchers like Carolyn Fang, associate director for Population Science, and Shannon Lynch, assistant professor in the Cancer Prevention and Control research program. They are investigating the caregiver burden as well as the role of sociodemographic factors in pancreatic cancer risk and outcomes.

"After doing this for five years, I can't do anything without my collaborators. We've taken it as far as meeting every other week and planning our clinical trials together to be able to integrate all these pillars," said Cukierman.

"Our goal is to find the science behind what we do and make breakthroughs," added Reddy. "Investigator-initiated trials are what's going to move that needle and push that envelope."

WINDOW OF OPPORTUNITY

Perhaps the best examples of how this cross-pollination forms the foundation of translational medicine are the institute's clinical trials, through which researchers are developing and evaluating a number of new therapies.

"The idea behind these trials is that we have to design concepts for which we have drugs and vice versa," said Astsaturov. "In other words, we need mechanistic rationale for these drugs to understand how a certain drug is relevant to a specific mechanism. We started building a portfolio of clinical trials that are intimately linked to the ongoing basic and translational research in our group."

Among these studies is one that is of a type referred to as a "window trial." The trial is exploring the reprogramming of the supportive tissue of the pancreas, called the stroma, to its natural tumor-suppressive state as it undergoes changes during cancer development and as a result of antitumor therapies. Astsaturov is working on the study with Dotan.

"Patients with pancreatic cancer who can be surgically treated typically undergo total neoadjuvant therapy, which is treatment with chemotherapy and radiation before the tumor is removed, following which they have to wait four to six weeks for their bodies to recover prior to undergoing surgery," said Astsaturov.

This period is viewed by researchers as a "window of opportunity" to test new tools to return cancer tissue to a

ASTSATUROV: ED CUNICELLI; REDDY: DAVID DEBALKO

natural state of cancer suppression and prevent regrowth of cancer cells after chemotherapy. During this period, patients receive a combination of drugs. Tumor samples are then taken during surgery, examined, and compared against patients who did not receive the drug combination.

This clinical trial, funded by the National Institutes of Health, is examining the effectiveness of combining paricalcitol (vitamin D), the malaria drug hydroxychloroquine, and losartan, a drug used to treat high blood pressure. The researchers decided to test this combination after it was used by a physician who was a long-term survivor of metastatic pancreatic cancer and published his experience in 2016. The Fox Chase team believes, based on this research, that using the combination may slow the progression of disease in pancreatic cancer patients. The trial started in August of 2021.

"We want to learn whether cancer cells survive this initial treatment. If they do, we want to know what these cells depend on to survive," said Astsaturov. "This is a big problem in pancreatic cancer, because these cells will survive beyond chemotherapy and the mechanism isn't clear."

"What makes this cancer institute unique is the collaborative efforts amongst leaders in each of their own disciplines with one common goal, the integration of science and patient-directed care."

—**SANJAY REDDY**, CO-DIRECTOR, MARVIN AND CONCETTA GREENBERG PANCREATIC CANCER INSTITUTE

Astsaturov said researchers can use advanced methods of genomics, which studies a person's genes and their interaction with the environment, to be able to identify the ways this resistance functions.

METHODS THAT MATTER

Another clinical trial at the institute is investigating other treatment options for pancreatic adenocarcinoma—the most common type of pancreatic cancer. Intact stroma, the cells and tissues that support and give structure to bodily tissues, is known to suppress tumor onset. It can also be altered to foster tumor development and metastasis, the spread of cancer cells to other parts of the body, as well as enabling drug resistance.

Chemotherapy and radiation followed by surgery is the backbone of treatment for pancreatic cancer, but researchers at Fox Chase found that radiation appeared to have an inflammatory effect on stroma, an effect that may actually spur the growth of cancer. In light of this finding, Cukierman, whose work focuses on stromal tissue, joined forces with Meyer.

The researchers are investigating the use of pulsed low-dose-rate radiation (PLDR) in a new pilot study. PLDR involves administering the standard amount of radiation to patients, but in smaller doses over a longer period of time, with the goal of minimizing the effects of radiation on healthy cells and possibly inhibiting the potential growth effects of standard radiation.

"When we treat patients with radiation, there is some repair or recovery in normal tissue, but that tissue never completely normalizes," said Meyer, who is the lead clinical investigator on the study. Previous research by Meyer showed that PLDR is not only safer and easier to tolerate than standard radiation, but could possibly be more effective.

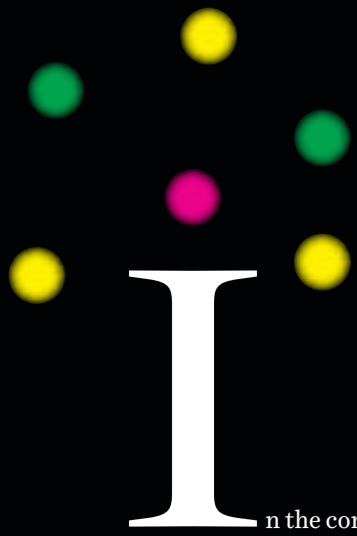
In this trial, 12 patients separated into two groups of six are treated with two different doses of PLDR that are administered in combination with chemotherapy. The treatment is then followed by standard surgery to remove the cancer after consultation with a surgeon, and samples are analyzed by researchers like Cukierman and Astsaturov to test whether the noncancerous pancreatic cells were effectively altered to benefit the patient. The trial is designed for newly diagnosed patients with localized pancreatic cancer who are candidates for surgery.

When they began preliminary tests, researchers found that inflammatory responses to radiation were decreased by using the PLDR method. Meyer said that because the standard dose of radiation for pancreatic cancer is not enough to control the cancer on its own, patients often have to undergo risky surgery. However, if patients could ultimately be treated with a higher dose of radiation, something that PLDR could allow, they might be spared surgery.

"I'm lucky that I get to collaborate with some really outstanding clinicians in other departments and we can figure out how to dovetail our different treatments, whether it's radiation and chemotherapy, or surgery," said Meyer. "We can work together to allow patients to get the most beneficial and safest treatment."

HITTING THE MARK

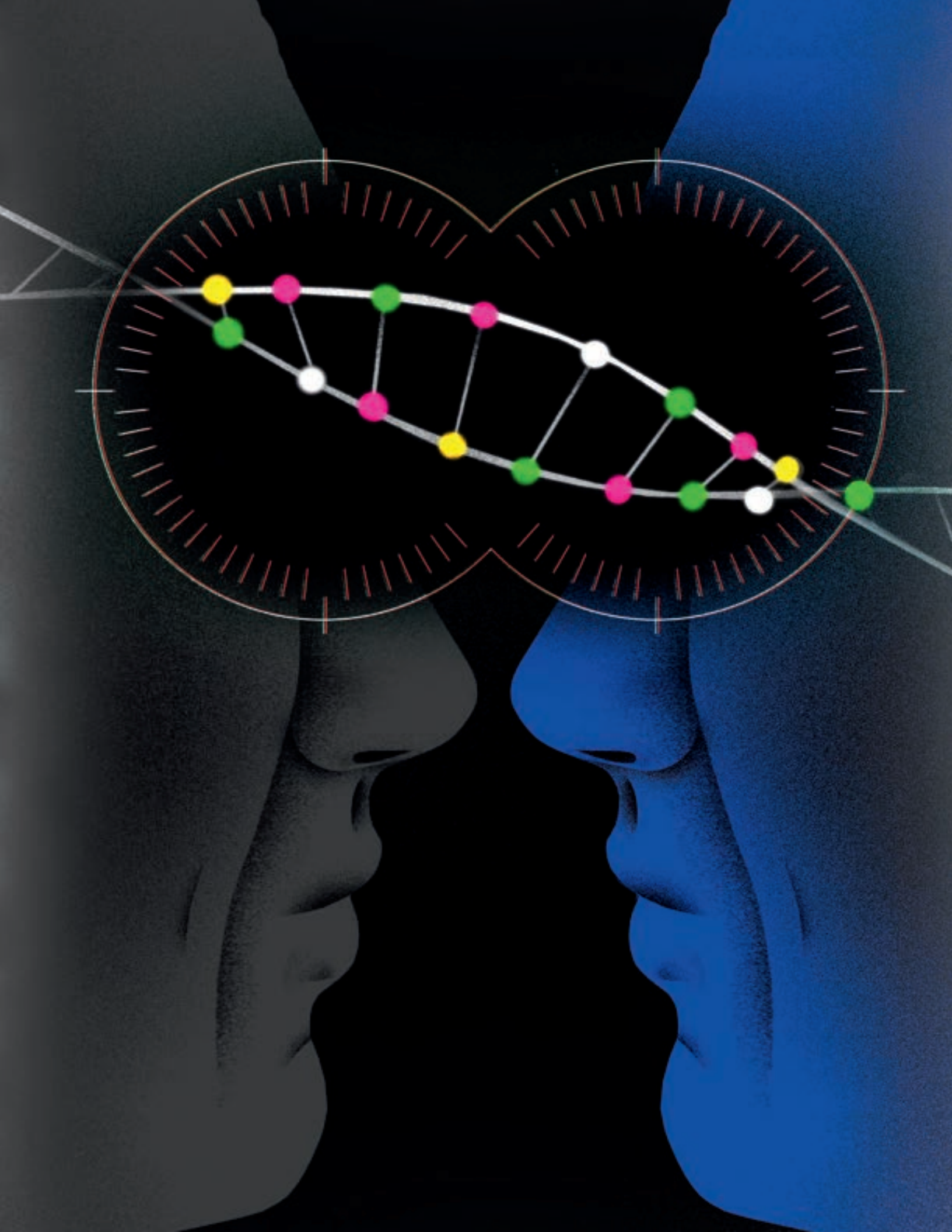
Researchers Collaborate to Identify Biomarkers and Refine Treatment



In the complex process of translational cancer research, it is crucial that clinicians and scientists work side by side when setting their sights on new and innovative methods for diagnosis and treatment. This work requires both the ingenuity of basic scientific research and clinical expertise to produce results that lead to tools such as diagnostic biomarkers.

Biomarkers are molecules found in blood, body fluid, or tissue that can be used as an indication of an abnormal process, such as cancer occurring in the body. Over the last two decades, more and more research has been done to identify biomarkers that can detect cancers and their subtypes and help clinicians determine the course of treatment. Scientists at Fox Chase and Temple Health are constantly working to make strides in these areas so that patients not only have effective treatment options, but a better quality of life.

BY MARIAN AURIEMMA
ILLUSTRATION BY BRIAN STAUFFER



RETAINING QUALITY OF LIFE

One area at Fox Chase where translational research on the use of biomarkers is in full force is the field of bladder cancer. Recently, researchers completed and reported results on the RETAIN 1 trial, which focused on individuals with muscle-invasive bladder cancer.

The standard treatment for this type of cancer is chemotherapy followed by surgery to remove the bladder. The RETAIN trial attempted to use diagnostic biomarkers to determine whether some of these patients could be spared removal of their bladder and be effectively treated with chemotherapy alone.

"Before patients started chemotherapy, we looked at their tissue samples and analyzed the DNA mutations in that specimen," said Elizabeth Plimack, a medical oncologist and Deputy Director of Fox Chase. "We were wondering if there were any clues in the specimen that could tell us who would do well and who would not. There were four genes that showed up that indicated that if a patient had these genes they would have a really good result from surgery."

With these findings, researchers aimed to see if it was possible to use those genes to also determine which patients would be more responsive to chemotherapy, thus sparing them removal of their bladder and allowing their condition to be monitored by their physician.

"There is clearly a group of people who are benefitting from not having their bladder removed. What we need to improve upon is finding the right patients. Based on our experience, we are looking to make that improvement in RETAIN 2," said Daniel Geynisman, head of the RETAIN trial and chief of the Division of Genitourinary Medical Oncology.

In RETAIN 2, the goal is still allowing patients to keep their bladders, but in addition to chemotherapy, patients will also receive the immunotherapy drug nivolumab. Immunotherapies are drugs that jumpstart the body's immune system to fight cancer.

"The rationale behind this combined therapy comes from some translational work that has been presented by several groups," said Pooja Ghatalia, a medical oncologist at Fox Chase who is taking part in the trial. "What they have found is that when patients receive a combination of this immunotherapy drug and chemotherapy, it can increase the chances of those patients responding well."

While these patients receive the combined therapy, researchers will check their tumor tissue for the mutations identified in RETAIN 1. If they have those mutations and no residual disease at the completion of treatment they have the option of keeping their bladder.

URINE BIOPSIES CHANGING DIAGNOSIS

Tumor tissue samples aren't the only way researchers at Fox Chase are investigating biomarkers in bladder cancer. In a collaboration with several clinical departments, Philip Abbosh, a researcher in the Molecular Therapeutics research program, has been working on a diagnostic urine test that will determine if bladder cancer patients have residual disease simply by using a biomarker.

"The aim of this work is to develop a dynamic test that enhances clinical staging as currently performed. When a patient has localized disease and has been treated for bladder cancer, sometimes it can be difficult to determine if the patient still has bladder cancer or not," said Abbosh.

The test captures both DNA that are released when tumor cells break open inside the bladder and DNA from whole tumor cells and normal cells that slough off the walls of the bladder and into the urine. Researchers can then use that DNA to analyze the genetics of the tumor.

"After therapy, the clinical assessment of the residual disease status should always dictate what therapy the patient gets next, if any," said Abbosh. "As one can imagine, making the wrong disease status call either way is not desirable if the decision being made is whether or not to proceed with surgery. This urine test is a way to try and enhance diagnosing residual disease after therapy in these patients."

> "We find that when you join forces with basic science researchers and those who work in patient care, you bridge these gaps and bring translation to the clinic."
>
> —**SANJEEVANI ARORA**, CANCER PREVENTION AND CONTROL RESEARCH PROGRAM

This method of monitoring bladder cancer patients is less invasive than current methods. Its potential for higher sensitivity is promising as well for tumors that are very small or hard to identify with a camera or when reviewing a CT scan, two common methods of detection.

Abbosh and colleagues will continue this work by analyzing urine from bladder cancer patients treated in five different clinical trials, including RETAIN 1 and RETAIN 2.

But it is not just patients with bladder cancer who can benefit from the translational work being conducted at Fox Chase. New approaches to identifying risks are also necessary for locally advanced rectal cancer patients who face chemoradiation therapy and surgery.

With this in mind, Sanjeevani Arora, an assistant professor in the Cancer Prevention and Control research program, is conducting a study to validate biomarkers of DNA damage repair. The aim for this biomarker is to potentially predict the effectiveness of chemoradiation before surgery for locally

Temple researcher Nathaniel Snyder (left) believes that studying the metabolism of cancer cells will yield new diagnostic tools. Philip Abbosh of Fox Chase (above) is working to develop a urine test that can determine if patients still have bladder cancer after treatment.

advanced stage rectal cancer patients.

"All of these patients get chemotherapy and radiation therapy prior to surgery, and the response is very variable among patients," said Arora. "There currently is no clinical biomarker that would indicate which patients would have a complete or poor response. The problem is that all patients will be exposed to this toxic therapy but will not gain equal benefit from it."

Results from the study indicate that the capacity for DNA damage repair may predict how much a patient could benefit from chemoradiation before surgery. This finding can assist researchers in selecting the appropriate patient for certain treatments, but Arora said studies in a larger population of rectal cancer patients are necessary.

Arora and her team collaborated on the study with experts from multiple areas, including the Department of Pathology and the High Throughput Screening Facility, which offer services that support basic research. She also worked closely with Joshua Meyer, vice chair of Translational Research for the Department of Radiation Oncology, to develop clinical applications for the findings.

"We find that when you join forces with basic science researchers and those who work in patient care, you bridge these gaps and bring translation to the clinic," said Arora.

REWIRING CANCER'S METABOLISM

This collaborative translational work is not just confined to Fox Chase, however. Nathaniel Snyder, associate professor for the Department of Cardiovascular Sciences and the Center for Metabolic Disease Research at the Lewis Katz School of Medicine at Temple University, is working alongside Fox Chase researchers to develop a new understanding of how cancer cells function. They're hoping the findings can be moved to the clinic to benefit patients.

Snyder's lab studies what he calls the "compartmentalization of metabolism" and works with Fox Chase researchers to determine how it plays a role in cancer.

"My lab looks at how, within the different compartments of a cell, metabolism is structured and separated. In a lot of cancers, the metabolism is basically rewired according to the environment it's growing in to suit its needs."

Snyder's lab is currently working with Vladimir Kolenko, an associate research professor in the Cancer Signaling and Epigenetics research program at Fox Chase, on studies involving prostate cancer and what happens when a patient undergoes androgen deprivation therapy, a common prostate cancer treatment that is used to suppress or block the production or action of male hormones. "We want to see how cancer cells evade that androgen deprivation by rewiring their metabolism," said Snyder.

He is also working with Lori Rink, assistant professor in the Molecular Therapeutics research program at Fox Chase, in a study involving a subset of Gastrointestinal Stromal Tumors (GIST), which is one of Rink's research specialties. These tumors have a rare mutation in a metabolic enzyme. Snyder said it is not known what the mutation does or how they can target it, but answering that question could open the door to helping patients with what is currently an untreatable condition.

"What's great is that most of the techniques we use are adapted from things that can be readily adapted to the clinic, like metabolic imaging and mass spectrometry, a tool used to identify chemical substances. We just need to figure out what enzymes to go after and how to target them in the right cancer," said Snyder.

"Cancer metabolism especially is one of the places I think we are going to make the biggest gains the most quickly because of the unique ways different cancers rewire their metabolism," he added.

SNYDER: JOSEPH V. LABOLITO; ABBOSH: THOMAS C. STEPHANO

THE WHITE-GLOVE TREATMENT

BY ALLISON L. GOLDSTEIN

Bhavesh "Bob" Desai has always been a healthy guy—no abnormal test results, no blood sugar issues, nothing. So when, at the age of 56, he and his wife, Gurpreet Kaur, came back after an evening at a friend's house and he started feeling pain in his abdomen, he assumed it would pass. He has a high pain tolerance, but eventually it got so bad that he woke his wife up at 3 a.m. to drive him to the hospital.

It turned out he had gallstones and needed to have his gallbladder removed. However, because his gallbladder was infected, the surgery couldn't be done right away. The hospital sent him home for a few weeks with a bag attached to his abdomen to drain out the fluid and resolve the infection.

When he came back and had the operation, the surgeon wasn't able to remove his whole gallbladder because the part touching his liver had hardened, which suggested cancer. "He ordered a biopsy, and that's when it was confirmed that I had gallbladder cancer," Desai said.

Because they had some reservations about the treatment he'd received at the first hospital he was treated at, Desai and his wife decided to get a second opinion. He has a cousin in Detroit who is an oncologist, and he helped Desai and his wife come up with the right questions to ask as they visited other hospitals near where they live in Pennsburg, Pennsylvania.

Some of the places they went just didn't feel right. "If you walk in and the first thing the doctor says to you is, 'We're going to cut you open,' it's pretty unnerving," Desai said. That's why, when they came to Fox Chase Cancer Center, they knew it would be their last stop. Even though they had an appointment scheduled at another hospital, they cancelled it once they met the doctors at Fox Chase.

> "The people at Fox Chase know that cancer patients need to be handled with compassion, and they really do give you white-glove treatment. It makes you feel confident that things will go well."
>
> —**BHAVESH "BOB" DESAI**, GALLBLADDER CANCER SURVIVOR

Desai and his wife had an appointment with surgical oncologist Jason Castellanos. He and the other oncologists went over the treatment course they were proposing with them step by step. The physicians showed them slides and explained what they intended to do, and why, in great detail. "I shared everything with my cousin, and he, my wife, and I all agreed that Fox Chase was where I would get treatment," Desai said.

According to the tests Castellanos ordered, the cancer hadn't spread, but Desai still had gallstones in what remained of his gallbladder. Therefore, he needed two more procedures: one to take out the gallstones and a surgery with Castellanos to take out the rest of his gallbladder and a nearby section of liver to make sure the cancer wouldn't spread.

Desai said that for each procedure he felt very well cared for from start to finish. Every person at Fox Chase, starting with the receptionist and all the way up to his

COLIN LENTON

oncologist, Namrata Vijayvergia, and Castellanos, was amazing. "The people at Fox Chase know that cancer patients need to be handled with compassion, and they really do give you white-glove treatment. It makes you feel confident that things will go well. In fact, I felt so confident that while many patients have elevated blood pressure right before surgery, mine was completely normal," Desai said.

Feeling so comfortable with Castellanos was key, Desai added. As he was being wheeled into his surgery, Desai asked Castellanos to take a picture of whatever was removed from his body during the surgery. "He asked me if I was sure—I was—and he did it. I still have that picture," Desai said.

All of Desai's postsurgery tests came back clean, so he's back to working in the automotive business as a sales manager, the same work he did before his diagnosis. He enjoys spending time with his wife and daughters and their children. "The only difference now is a four-by-four-inch scar on my stomach. That's it," Desai said.

"My number one piece of advice to anyone going through this is don't just go by what the first doctor says," he added. "You need to get second opinions and you need to make Fox Chase your last stop."

A SCIENTIST WITHOUT BORDERS

BY SARAH JAYNE HUGHES

Four languages, three countries, the support of her family, and 20 years at Fox Chase Cancer Center have made professor Edna "Eti" Cukierman the scientist she is today. This includes leading a team of researchers and her role as co-director of the Marvin and Concetta Greenberg Pancreatic Cancer Institute. Cukierman is a proud second-generation Mexican who grew up speaking Spanish and attended a private Jewish grade school. It was there that she was taught Yiddish as her second and Hebrew as her third language. Once in high school, Cukierman began learning English.

Unsure of her career path, Cukierman took a gap year in Israel after high school. It was there that she met her Israeli husband, Mario Cukierman, who was born in Uruguay. The two have been together now for 36 years. After they married, Cukierman took several more courses in Hebrew before attending the Technion-Israel Institute of Technology, where she earned an undergraduate degree in biology, a master's in biochemistry, and a doctorate in molecular and cell biology.

"I think I was in the right place at the right time," said Cukierman, who is also a co-leader of the Cancer Signaling and Epigenetics research program at Fox Chase. During her doctoral work, she published a paper in the prestigious journal *Science* on her discovery of a new enzyme, the ARF1 GTPase-activating protein—ARF1-GAP. It was the first in a now-abundant family of ARF-GAPs, which are key enzymes that regulate how vesicles—tiny membranous sacs that transport biomaterials—move within cells.

During her doctoral studies, Cukierman also gave birth to her two sons, Gil and Amit. So when it came time to decide where to go for her postdoctoral work, she and her husband had a family to consider. They decided to move to the Washington, D.C., area, where she completed her postdoctoral research at the National Institute of Dental and Craniofacial Research at the National Institutes of Health, while her husband worked for the Israeli embassy.

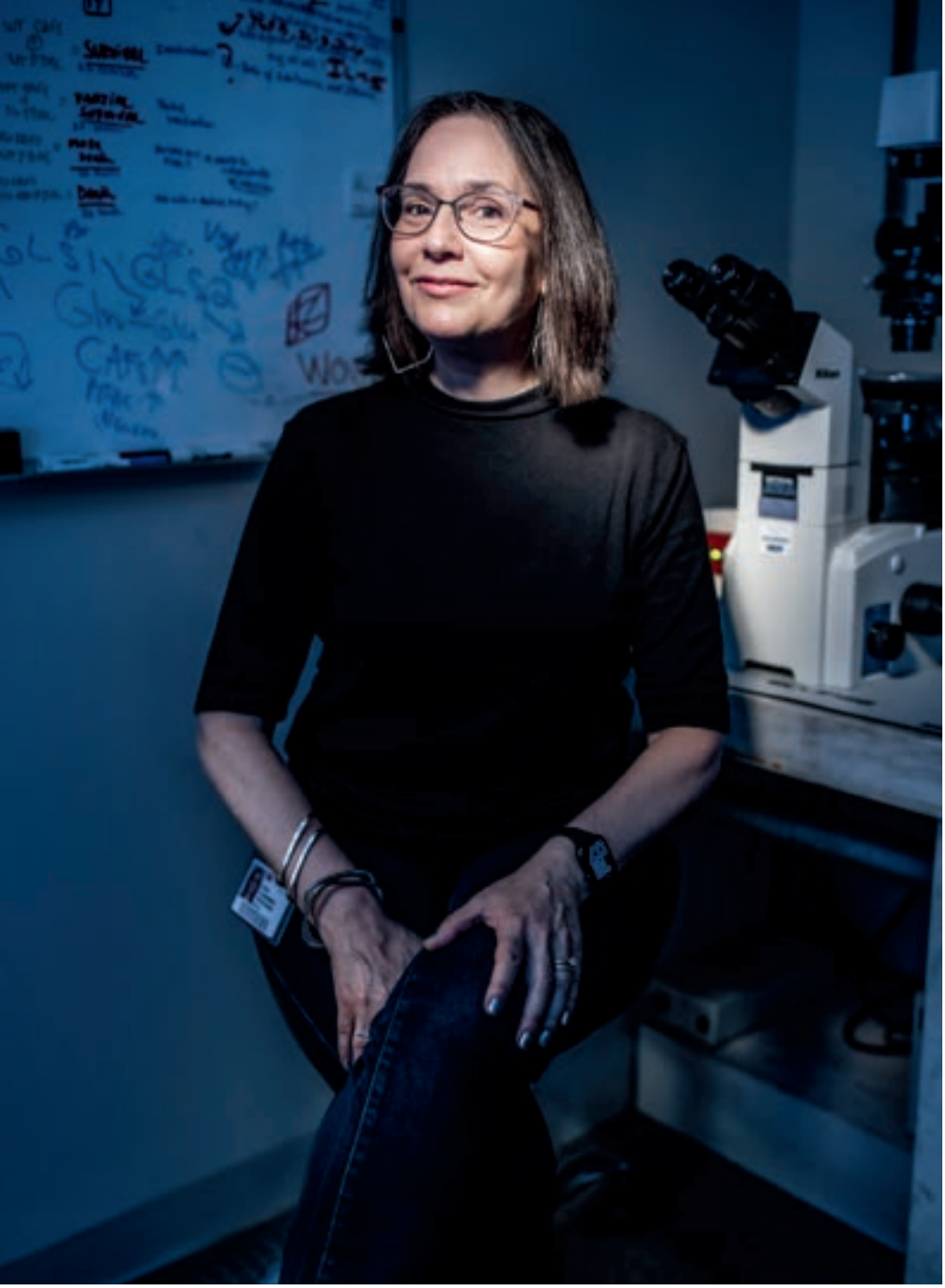
"It took a lot of teamwork," said Cukierman, but there was an upside. "Having kids, I believe, made me a better scientist, because it forced me to be much more organized and learn how to prioritize, which really expanded my professional skills."

Cukierman said that during her postdoctoral work, being curious was her biggest asset. "By thinking that way, I was able to uncover a new adhesion structure, which was also published in *Science*, between fibroblastic cells and the natural fibrous substrates these cells reside within," she said.

When she first came to Fox Chase, Cukierman knew nothing about cancer research, but she knew a great deal about functional fibroblastic cell/substrate units, which are key to understanding the biology that regulates the cancer's immediate neighborhood, known as the tumor microenvironment.

Cukierman's lab has been able to unravel and begin understanding the cancer-associated fibroblastic functional units of the tumor microenvironment and how they modulate cancer development and deter the immune system from killing cancer cells. A key piece of work was a paper

> "My career decisions are never solely scientifically based; they have always been a family team effort."
>
> —**EDNA "ETI" CUKIERMAN**, CO-DIRECTOR, MARVIN AND CONCETTA GREENBERG PANCREATIC CANCER INSTITUTE



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in *Cancer Discovery* in which her lab reported the discovery of Netrin G1 as a potential new target. They found that by inhibiting the Netrin G1 protein they could harness the natural tumor-suppressive functions of fibroblastic units without eliminating them, which would otherwise accelerate tumor progression. This discovery could help starve cancer cells in patients with pancreatic cancer and allow the immune system to attack their tumors.

Cukierman said that after years of considering herself a basic scientist, it is rewarding to see that discoveries from her team have potential applications in the clinic. In fact, her lab's discoveries now play key roles in ongoing and future clinical trials to test whether the tumor microenvironment can indeed be modulated in order to regain its natural tumor-suppressing function. The hope is to one day benefit pancreatic and other cancer patients.

Although she has had many influences in her groundbreaking work, Cukierman credits its Fox Chase legend Dr. Beatrice Mintz for teaching her how noncancerous cells in the microenvironment, where cancer could develop, are naturally restrictive of tumor development. The idea that something must happen to those noncancerous cells in their immediate environment to spark tumor development and facilitate cancer cell growth fascinated her. Dr. Alfred Knudson, another Fox Chase giant, inspired Cukierman and ingrained in her early on the idea that tumor development is also stalled by natural tumor-suppressive genes.

In addition to past figures like Mintz and Knudson, one of the many things Cukierman loves about Fox Chase is the family feel and the mentorship opportunities she has with noted scientists that she works with now. "I have had mentors like Ann Skalka, Margie Clapper, Erica Golemis, Jon Chernoff, and Glenn Rall who have been my role models," said Cukierman. She returns the time and advice they have given her by mentoring several young faculty members.

"My career decisions are never solely scientifically based; they have always been a family team effort," said Cukierman. "But I consider myself the luckiest person, because those family based decisions and ongoing support made me who I am today."

A COMMITMENT TO COMMUNITY

BY ANDREW BECKER

Although many companies embrace philanthropy as part of their corporate culture, a few have emerged as genuine leaders in community support. Wawa, the Pennsylvania-based convenience store chain, is one of those companies that stands out for its history of philanthropy, the involvement of employees, and its commitment to Fox Chase Cancer Center. The company has been engaged in improving lives in the communities where it operates since well before the term "corporate social responsibility" was coined.

"Giving back is in our DNA," said Jay Culotta, chair of The Wawa Foundation, the company's philanthropic arm. In addition to his work with the foundation, Culotta recently marked 25 years in his full-time job as treasurer of Wawa Inc. He said that while Wawa's namesake stores opened in 1964, the company was founded more than 200 years ago and has been committed to making an impact in the world almost as long. "Wawa's history of supporting charitable causes goes back to at least the 1850s," he said.

As the company evolved, so did its commitment to community. At the beginning, Wawa's charitable efforts were driven by the Wood family, the founders and majority owners. In recent decades, associates at all levels of the company have taken the lead.

Over the past several years, those efforts have included generous support for a variety of initiatives at Fox Chase. Wawa has donated funds to support breast cancer research, updates to the infusion room, and to help purchase a next-generation mobile screening unit. Wawa has also partnered with Fox Chase for several annual matching gift campaigns, pledging to match the community's contributions dollar for dollar. The 2021 campaign was the cancer center's most successful matching campaign ever.

The financial support has been generous, impactful, and varied. So have the personal connections. During the initial phase of the COVID-19 pandemic, when doctors, nurses, and other frontline personnel were working around the clock under the most difficult circumstances, local Wawa stores were among the businesses that delivered free meals to keep them going.

"Supporting individuals in treatment and survivorship at Fox Chase is a no-brainer, and so was helping to feed frontline healthcare providers when the pandemic began," Culotta said. "These opportunities to partner with Fox Chase fit perfectly with our philosophy of contributing to causes related to health, hunger, and everyday heroes."

> "Supporting individuals in treatment and survivorship at Fox Chase is a no-brainer, and so was helping to feed frontline healthcare providers when the pandemic began."
>
> —**JAY CULOTTA**, CHAIR, THE WAWA FOUNDATION

While giving back is in Wawa's DNA, it's in Culotta's too. He's been involved with Wawa's charitable efforts for most of his long tenure with the company, first as a member of the Charities Committee at Wawa, and since

Left: During the COVID-19 pandemic, Wawa supported Fox Chase staff with free meals. Above: Jay Culotta, chair of the Wawa Foundation, with his daughter Hannah, who is a Wawa employee.

PHOTOS COURTESY OF FOX CHASE INSTITUTIONAL ADVANCEMENT; JAY CULOTTA

2014 with The Wawa Foundation when it became a separate entity. "When I became a father to a child with special needs, my family became involved in a lot of community work, and I realized the intrinsic value of giving back." His daughter Hannah, now an adult, is also a Wawa associate.

The Wawa Foundation's mission is to organize and support the company's charitable giving and philanthropic activities. The board, which includes 13 corporate employees, receives as many as 1,000 requests for funding or product support each month and funds thousands of grants and other charitable gifts every year. The Fox Chase relationship began with such a request in 2014.

"The foundation's work is a big undertaking, but it's easy to commit to the extra hours, because it's so rewarding," Culotta said. "The initial goal of the foundation was to donate $50 million to various causes over five years, but we surpassed that total in less than four years."

Currently, Wawa and The Wawa Foundation donate about $16 million a year to its many partners, which include seven large national partners and dozens of regional partners and grantees. Depending on the need, gifts can range from $500 up to hundreds of thousands of dollars. Individual stores also provide in-kind support to local events.

Although the relationship between Wawa and Fox Chase is relatively young, both organizations see a bright future working together to impact many lives. "Our support of Fox Chase is a true expression of our desire to be as helpful as we can be to the people in our community," Culotta said.

CHERNOFF AWARDED BREAST CANCER RESEARCH GRANT

Jonathan Chernoff, Cancer Center Director at Fox Chase Cancer Center, was recently awarded a $50,000 grant from the Pennsylvania Breast Cancer Coalition.

This one-year grant will provide funding for Chernoff's research into two specific genes on chromosome 11 that become amplified in many breast cancer patients. "This grant will allow me to pursue promising preliminary data that points to new strategies for treating breast cancer. It could lead to new therapeutic approaches in a significant number of breast cancer patients," said Chernoff, who is also the Stanley P. Reimann Chair in Oncology Research.

Chernoff's lab focuses on uncovering the roles of protein phosphorylation in governing two fundamental aspects of cancer biology—cell proliferation and cell movement.

ELIZABETH PLIMACK APPOINTED DEPUTY DIRECTOR

Elizabeth Plimack, chief of the Division of Genitourinary Medical Oncology and professor in the Department of Hematology/Oncology at Fox Chase Cancer Center, has been appointed Deputy Director.

"Conducting world-class cancer science is an integral part of our Fox Chase mission and identity as a National Cancer Institute-designated Comprehensive Cancer Center. Strong leadership in this area is critical to supporting our research enterprise and to promoting progress and success. That's why I am so pleased to announce the appointment of Dr. Plimack to this key position," said Jonathan Chernoff, Cancer Center Director at Fox Chase.

Plimack will oversee the Clinical and Translational Research Plan as she takes on this newly created role. Her primary areas of focus will include:

Programmatic scientific strategy, in which she will lead the growth of interdisciplinary translational science by building alliances across clinical disciplines and among clinical and basic science faculty.

Further development of the Fox Chase Bladder Cancer Program towards an integrated and collaborative research program.

Development of institutional diversity, equity, and inclusion (DEI) initiatives by addressing DEI as an integral part of the Fox Chase Cancer Center Support Grant renewal and by improving the Fox Chase culture to aid retention and recruitment of women and Underrepresented in Medicine faculty and staff.

NURSES DEVELOP TOOL TO BETTER MONITOR ORAL CHEMOTHERAPY

Nurses at Fox Chase successfully implemented an electronic medical record tool to improve compliance documentation for patients taking oral chemotherapy drugs.

The success of this program was presented as part of the 47th Annual Oncology Nursing Society Congress.

"In recent years we realized that there is an abundance of oral chemotherapy prescriptions being prescribed to our patients that required follow-up," said Maria Market, of the Ambulatory Clinic at Fox Chase.

Market and her colleague Allison Ward designed a tool to provide a standard form for documenting the treatment plan, education, and monitoring for oral chemotherapy.

A pilot study found that the number of patients contacted after the start of oral chemotherapy increased from 4% to 35% and documented discussions addressing adherence increased from zero to 78%.

"These are powerful drugs that we are sending home with our patients," Market said. "By implementing this tool we were able to increase patient safety."

CHERNOFF: COURTESY OF FOX CHASE CANCER CENTER; PLIMACK: COLIN LENTON

JOHN KARANICOLAS AWARDED UNIVERSITY CITY SCIENCE CENTER GRANT

John Karanicolas, co-leader of the Molecular Therapeutics research program, was awarded a $200,000 grant as part of the University City Science Center's QED Proof-of-Concept Program. The grant will fund research into developing antibodies that could be activated selectively in a tumor by a small molecule.

"Antibodies are always binding to their specific target, and this can be used for many therapeutic purposes. But the problem can be that in certain cases the target of the antibodies is present everywhere in the body and not just in the tumor. This can lead to toxicity or immune-related adverse events," said Karanicolas.

"The key to our idea is that the antibody will recognize its target inside the tumor and provide therapeutic efficacy, but will not bind to the same target away from the tumor. If successful, this will eliminate the immune-related adverse events," he added.

The funding recommendation for the project, which was one of three selected, was made by a team of investors and industry experts. The team reviewed the project's proof-of-concept plan and decided that it had high potential to dramatically improve the standard of care in life sciences over existing technologies on the market.

EAST NORRITON NURSES RECEIVE EXCELLENCE IN NURSING AWARD

Main Line Today has honored six Fox Chase Cancer Center – East Norriton nurses with their 2022 Excellence in Nursing Award. These exceptional professionals were nominated for their dedication and contributions throughout 2021. Fellow nurses from the region voted on the selections.

"This distinction is a great honor not only for the East Norriton campus, but all of Fox Chase Cancer Center," said Anna Liza Rodriguez, chief nursing officer and vice president of nursing and patient services at Fox Chase.

The following nurses were honored: Kimberly Berman, Valerie Heron, Nicolas Hoover, Carol Shellock, Christa Shine, and Maureen Sims.

Main Line Today is a regional magazine focusing on Philadelphia's suburban Main Line and western suburbs. The nurses were honored in the magazine's May 2022 issue.

Fox Chase's East Norriton facility opened in May of 2018 in Montgomery County, Pennsylvania, and offers access to Fox Chase's specialized team of surgical oncologists, radiation oncologists, hematologists/oncologists, and genetic counselors in a community setting, allowing individuals to be treated closer to home.

PHOTOS COURTESY OF FOX CHASE CANCER CENTER

Jason Castellanos was named a 2022 Top Physician Under 40 by the Pennsylvania Medical Society. To be nominated, physicians must practice in Pennsylvania and be under the age of 40.

Zachary Frosch received a Young Investigator Award from the National Comprehensive Cancer Network (NCCN) and the NCCN Foundation. Frosch, who is one of seven recipients of the award, will receive up to $150,000 in funding over two years.

Kristen Manley was named a 2022 Top Physician Under 40 by the Pennsylvania Medical Society. To be nominated, physicians must practice in Pennsylvania and be under the age of 40. Winners were selected by a committee of PAMED members.

Suzanne M. Miller received a research grant from the Prevent Cancer Foundation to support a project to test whether text messaging can effectively reduce urban cervical cancer disparities.

Sameer Patel was recently inducted into the American Association of Plastic Surgeons. To earn this honor, physicians must prove significant contributions to plastic surgery through academic achievement, teaching, and research.

JOSE AND IRMA RUSSO: A POWER COUPLE IN SCIENTIFIC DISCOVERY

BY MARIAN DENNIS

When Jose Russo began his career in cancer research at the National University of Cuyo in Mendoza, Argentina, he sparked more than just a career in medicine. While there, he met a woman whose passion for science matched his own. Irma Russo (then Alvarez) was also studying medicine when their paths crossed, and they began not only a life of love and companionship, but a decades-long journey in scientific discovery. Over 30 of those years were spent at Fox Chase Cancer Center.

Jose and Irma were married in 1971 and moved to the United States to pursue research as part of a fellowship for the Rockefeller Foundation, a research organization aimed at solving global challenges in medicine and public health. Shortly after, they moved on to the Michigan Cancer Foundation, now the Karmanos Cancer Institute, in Detroit.

The couple's work at this center would become the basis of their lifelong mission of researching breast cancer, its causes, and potential means of prevention. As a team, they were pioneers in understanding how pregnancy mediates breast cancer prevention.

The couple's work with the pregnancy hormone human chorionic gonadotropin in preventing breast cancer led to a clinical trial that is now underway internationally. "I'm glad that the trials are moving along. That was something I know my dad really wanted to be able to see through, so it's really great to see," said Patricia Russo, Jose and Irma's daughter, who also pursued a career in medicine.

"They really were perfect for each other and had this really special bond. I remember we would be sitting at the dinner table and they would be talking about some experiment, which as a kid I didn't understand. But that was just another typical dinner."

In 1991, Jose and Irma moved their breast cancer research to Fox Chase Cancer Center. Jose served as chair of the Department of Pathology and director of the Breast Cancer Research Laboratory, where Irma was director of the Molecular Endocrinology section.

"Jose and Irma were a quiet couple who were always together," said Joseph Testa, chief of Genomic Medicine at Fox Chase and a friend of the two. "They were an incredible fit and had a truly wonderful life together. They were in it as a team. How many people get to share their science with another person?"

Their humble nature and dedication to their field extended through their careers to touch the lives of the over 100 cancer researchers they mentored. Patricia described their lab environment as a second home, recalling her time working with her parents there.

"They really fostered a family atmosphere in the lab. They both felt it was very important to have the patience to teach people and guide them through. ... Those researchers are still like a second family," she said.

> "They really fostered a family atmosphere in the lab. ... Those researchers are still like a second family."
>
> —**PATRICIA RUSSO**, DAUGHTER OF JOSE AND IRMA RUSSO

During her tenure at Fox Chase, Irma remained devoted to the mission of understanding the cellular and molecular basis of breast cancer until her death in 2013. In her honor, the Breast Cancer Research Laboratory at Fox Chase was named the Irma H. Russo, MD, Breast Cancer Research Laboratory.

Jose continued working until he was physically unable to do so, a week before his death in September 2021. At that time, he was a professor and director of the research laboratory that bore his wife's name.

PHOTO COURTESY OF FOX CHASE CANCER CENTER ARCHIVES

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